



# ACNEM TRAINING

## Colds, Flus & COVID-19: Can Supplements Help?

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## 1. COVID-19 Statistics

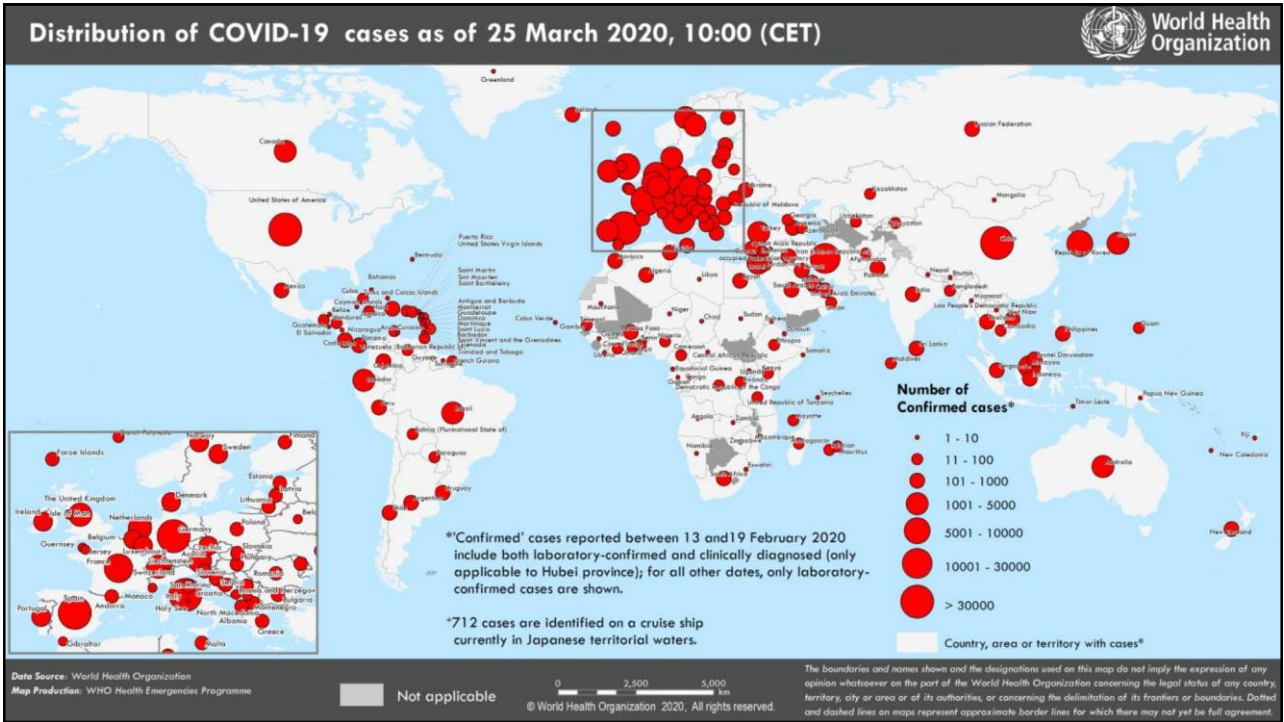
- Current pandemic with 414,179 cases (2252\* Australia), 18,440 **deaths** recorded worldwide in 190 countries to date (25 March 2020)
- 2252 cases in Australia, 8 deaths (WHO 2020, 25 March: [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200325-sitrep-65-covid-19.pdf?sfvrsn=2b74edd8\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200325-sitrep-65-covid-19.pdf?sfvrsn=2b74edd8_2))
- Those with compromised immune systems at risk
- Older people, people with pre-existing medical conditions (e.g. asthma, diabetes, heart disease) appear to be more vulnerable to becoming severely ill with the virus (WHO 2020).

Note: in video presentation, this figure was inadvertently reported as 1709 which was the previous day's figure.

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## 2. COVID-19 Pathology

- COVID-19 assoc with serious sequelae of pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), acute shock & multiple organ failure (Peng 2020; Chen et al. 2020; Wang et al. 2020)
- 99 patients at Wuhan hospital: 17% confirmed cases developed ARDS with 4% requiring mechanical ventilation & 4 % experiencing septic shock (Chen et al. 2020)



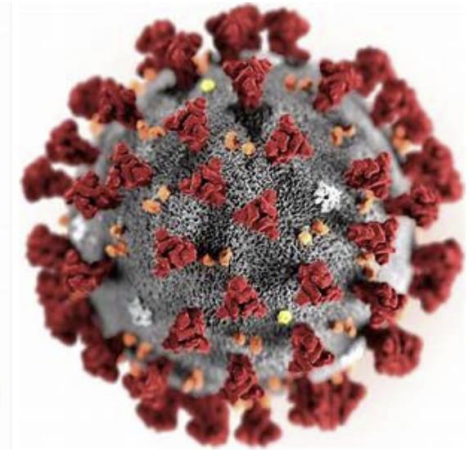
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# Acute Respiratory Distress Syndrome (ARDS)

- Characterised by severe hypoxia, uncontrolled inflammation, oxidative damage & damage to the alveolar-capillary barrier which can lead to death (Cheng et al. 2020)
- Viral infection causes 'cytokine storm' which activates lung capillary endothelial cells, leads to neutrophil infiltration & accumulation (damages alveolar capillaries), alveolar fluid accumulation & increased oxidative stress (Peng 2020; Cheng et al. 2020)
- Oxidative stress key factor in lung injury incl ALI & ARDS (Cheng et al. 2020)



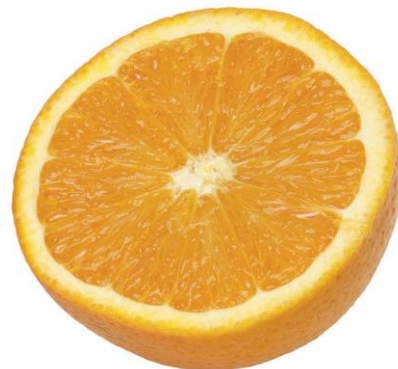
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## 3. Vitamin C & Respiratory Illness

- Animal studies: Vitamin C can reduce incidence & severity of bacterial & viral infections (Hemila & Chalker 2013)
- Vitamin C:
  - increases neutrophil phagocytosis & chemotaxis
  - increases macrophage migration
  - affects replication of viruses
  - affects production of interferons
  - enhances T & NK cell proliferation & modulates their functions
  - may increase antibody formation
  - powerful antioxidant, can protect various cells against oxidative stress during infection (Hemila & Chalker 2013; Nabzdyk & Bittner 2018)



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## How Does Vit C Help?

- Vitamin C accumulates in phagocytic cells, e.g. neutrophils & can enhance chemotaxis, phagocytosis, generation of ROS & ultimately bacterial & viral killing
- In monocytes (usually 1st immune cells mobilized in immune response to inflammation) Vit C documented to concentrate 80-fold (8,000%) above plasma levels (Evans et al. 1982)
- Vit C essential factor in production of anti-viral immune response during early phase of viral infection thru production of type I interferons (Kim et al. 2013), which up-regulates NK cell & cytotoxic T-lymphocyte activity (Madhusudana et al. 2004)
- Vit C can be used as an inactivating agent for RNA & DNA viruses, lessening viral infectivity (Jariwalla and Harakeh 1996; Byun and Jean 2011)
- Vit C can detoxify viral products that produce pain & inflammation (Harakek et al. 1990)
- Anti-viral effects demonstrated Influenza type A, HSV type 1 & poliovirus type 1 (Kuriyama et al. 2008)



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## In vivo research: Influenza

- **Research in chicken cells:** Vit C appears to interfere with spread of infection through a reduction in virus replication & virus infectivity (Bissell et al. 1980)
- Investigated if Vit C could regulate influenza virus infection in vivo **bGulo (-/-) mice** (like humans can't synthesize vitamin C)
- Vit C-insufficient *Gulo (-/-)* mice died w/in 1 week after intranasal inoculation of influenza virus (H3N2/Hongkong) cf. all wild-type & Vit C-sufficient *Gulo (-/-)* mice survived
- Vit C supplementation on a day after virus inoculation did not prevent death of Vit C-insufficient *Gulo (-/-)* mice
- Viral titer in lung from vitamin C-insufficient *Gulo (-/-)* mice 10 to 15-fold increased cf viral titer in wild type & vit C-sufficient *Gulo (-/-)* mice
- When *Gulo (-/-)* mice were supplemented with Vit C after virus inoculation, no definite suppression of viral replication observed
- Vit C concentration at initial states of influenza virus infection critical- the damages through replication of influenza viruses can be **effectively prevented when Vit C concentration sufficiently high at initial stage of viral infection** (Kim et al. 2013)



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## Evidence of Efficacy of Vit C Against Viral Infections

- High dose IV Vit C shown effective against viral infections:
  - Common cold rhinovirus (Hemila & Herman 1995)
  - Avian virus H1N1 (Ely 2007\*\*; Bissell et al. 1980\*)
  - Chikungunya (Gonzalez et al. 2014; Marcial-Vega et al. 2015);
  - Zika (Gonzalez et al. 2016)
  - ARDS (Fowler et al. 2017)
  - Influenza (Zarubaeva et al. 2017; Gonzales et al. 2018)
- Oral supplementation Vit C (doses > 3g) can prevent & treat respiratory & systemic infections (Carr & Maggini 2017)

\* In vitro study; \*\* commentary



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## Common Cold & Vitamin C: Meta-analysis

- Usually caused by resp viruses (rhino, corona, parainfluenza etc) (Hemila & Chalker 2013)
- Meta-analysis: common cold duration reduced by 8% in adults (17 RCTs) & 14% in children in those who took **Vit C regularly** (most studies, 1000mg/day), though in children who took 1-2g Vit C daily, cold duration was reduced 18%
- Severity of colds was also reduced in those who supplemented regularly (Hemila & Chalker 2013)



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# Case Report: IV Vit C & Influenza

## Demonstrated IV Vitamin C instrumental in recovery

- Tx of 25 yr old male Px with influenza, fever, aches, loss of 15 pounds weight
- Tx IV Vit C: 1,000 cc of lactated Ringer's solution containing 50g sodium ascorbate, infused over 1.5 hrs. Regimen was repeated: total of 3 infusions over 3 days.
- Morning after first IV, body strength improved greatly, no HAs; appetite improved after second IV
- Felt normal on Day 4. Vit C continued orally (2 g tid)
- Advised to take high potency multivitamin & mineral (1qd) + CoQ10 (100mg qd) on a regular basis orally.
- Echinacea (500 mg bid for ten days) (Gonzales et al. 2018)



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# Case Report: High Dose IV Vit C & Acute Respiratory Distress Syndrome (ARDS)

- Patient with virus-induced ARDS treated with high dose IV Vitamin C (200mg/kg per 24 h, total daily Vit C dosage divided equally into 4 doses infused every 6 h) initiated on Extra Corporeal Membrane Oxygenation day 1.
- Rapid resolution of lung injury, no evidence of post-ARDS fibro-proliferative sequelae
- Concluded: 'Intravenous vitamin C as a treatment for ARDS may open a new era of therapy for ARDS from many causes' (Fowler et al. 2017)



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## IV Vitamin C & Septic Shock

- Clinical studies report benefits of IV Vitamin C in septic shock including reduced mortality (Marik et al. 2017; Zabet et al. 2016)
- Study of 28 ICU Px's with sepsis & shock: 25mg/kg IV Vit C every 6 hours reduced amount of norepinephrine needed to maintain BP & reduced 28-day mortality to 14% (cf. 64% in control group not receiving IV Vit C) (Zabet et al. 2016)
- Meta-analysis (18 studies, administered orally in 7 trials [cardiac Pxs, 1-3g/day], IV in 11 trials [dose ranged from 0.5 to 110 g/day])
  - Vit C reduced length of ICU stay by almost 8% (12 RCTs, 6 oral, 6 IV)
  - All of the 6 oral admin trials used Vit C doses 1- 3 g/day. Vit C reduced length of ICU stay by 8.6% (95% CI: 3.0% to 14.0%;  $p = 0.003$ )
  - In 3 studies where Px's needed mechanical ventilation for >24 hours, Vit C shortened duration of this intervention by 18.2% (Hemilla & Chalker 2019)



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## IV Vitamin C & COVID-19

- China using high dose IV Vitamin C to treat patients with COVID-19 related ARDS
- March 2020 Shanghai government: official recommendation that COVID-19 should be treated with high doses of IV Vitamin C, with amounts varying according to severity of illness (Saul 2020)
- Shanghai Medical Association Consensus Statement recommends high dose IV Vit C for prevention & treatment of **cytokine storm**:  
<https://mp.weixin.qq.com/s/bF2YhJKiOfe1yimBc4XwOA>



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## Shanghai Medical Association: Expert consensus on comprehensive treatment of coronavirus disease in Shanghai 2019

- **(Two) treatment of light and ordinary patients:**
  - includes recommendation of high-dose vitamin C
- **(III) Organ function supportive treatment for severe and critically ill patients. 6. Prevention and treatment of cytokine storm:**
  - *'It is recommended to use large doses of vitamin C and unfractionated heparin. Large doses of vitamin C are injected intravenously at a dose of 100 to 200 mg / kg per day. The duration of continuous use is to significantly improve the oxygenation index. It is recommended to use large doses.'*

Shanghai Medical Association: Expert consensus on comprehensive treatment of coronavirus disease in Shanghai 2019. Available at: <https://mp.weixin.qq.com/s/bF2YhJKiOfe1yimBc4XwOA>

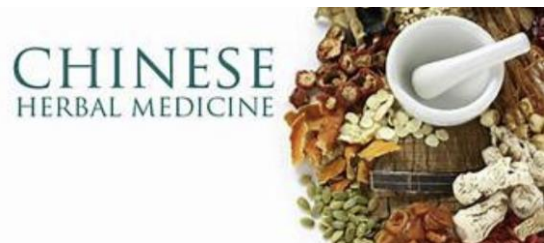


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## China: Combining Western & Chinese Medicine

- **Shanghai Medical Assoc Consensus Statement, Section (V) Treatment Plan of Integrated Traditional Chinese and Western Medicine**
  - *'The combination of traditional Chinese and western medicine for the treatment of new coronavirus pneumonia can improve the synergistic effect. For adult patients, the condition can be improved through TCM syndrome differentiation.'*



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## 4. Vitamin D & Respiratory Illness

- Observational studies report consistent independent associations b/n low serum concentrations of 25-hydroxyvitamin D (major circulating vitamin D metabolite) & susceptibility to acute respiratory tract infection (RTI) (Martineau et al. 2017)



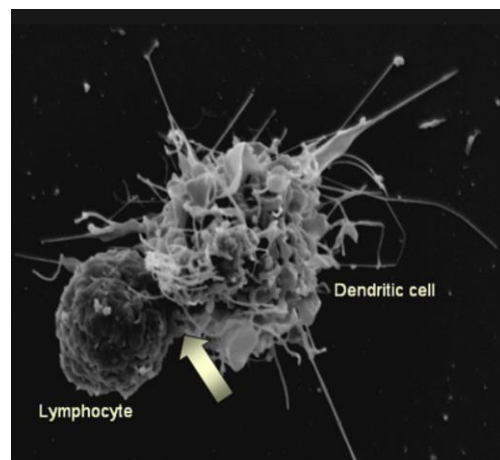
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## How Can Vitamin D Help?

- Vitamin D: major regulator of human immune responses
- Major mechanism - regulation of dendritic cell (DC) functions (DCs pivotal to instruction of immune responses in humans):
  - Several studies: Vit D Tx of human DCs elicits an anti-inflammatory/tolerogenic Th2/Treg-promoting, but not an inflammatory/ immunogenic Th1-promoting DC phenotype
  - Another study: Vit D promotes aspects of both pro-inflammatory & anti-inflammatory immune responses in humans (Sommer & Fabri 2015)



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## How Can Vitamin D Help in Respiratory Illness?

- Vitamin D may increase production of natural antibodies (Ralof 2006)
- 25-hydroxyvitamin D supports induction of anti-microbial peptides in response to viral & bacterial stimuli (Martineau et al. 2017)
- Vitamin D metabolites induce other innate antimicrobial effector mechanisms, incl. induction of autophagy & synthesis of reactive nitrogen intermediates & reactive oxygen intermediates (Martineau et al. 2017)



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## Meta-Analysis: Vitamin D & Acute Respiratory Tract Infections

- **Meta-analysis:** 5 clinical trials (doses Vit D 400 IU/day - 2000 IU/day, & in one study single parenteral dose of vitamin D given [100,000 IU])
- **Results:**
  - Events of respiratory tract infections significantly lower in Vitamin D group cf. control (OR 0.58, [95% CI 0.417 - 0.812],  $p=0.001$ ) (fixed & random effects models)
  - Children (2 studies): OR = 0.579 (0.416 - 0.805),  $P = 0.001$ , fixed & random effects model)
  - Adults (3 RCTs): OR = 0.653 (0.47 - 0.904),  $P = 0.010$  fixed effects model (random effects model, result NS, OR = 0.544 (0.278 - 1.063,  $P = 0.075$ ) (Charan et al. 2012)



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## Systematic Review: Vit D Supplementation & Acute Respiratory Tract Infection

- **Systematic review** 25 RCTs (11,321 participants aged 0-95 years) of Vit D supplementation: 12% reduction in participants experiencing at least one acute respiratory tract infection (OR 0.88, 95% CI 0.81-0.96).
- NNT to prevent one acute RTI = 33 (comparable with parenteral inactivated influenza vaccine [NNT 40 in adults, 28 in children to prevent influenza-like illness])
- Benefit greater in those receiving daily or weekly vitamin D without additional large bolus doses
- Protective effects greatest in severe deficiency (<25mmol/L baseline levels) (NNT = 4 with supplements to prevent 1 acute RTI) (Martineau et al. 2017)



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## Cochrane Review: Vit D Supplementation & Risk of Asthma

- Vitamin D supplementation reduces risk of severe asthma exacerbations (often precipitated by viral upper RTIs) & hospitalisations
- 7 RCTs (435 children) & 2 RCTs (658 adults) with mild-mod asthma
- Vitamin D
  - reduced rate of exacerbations requiring systemic corticosteroids (rate ratio 0.63, 95% CI 0.45-0.88; 680 participants; 3 studies)
  - decreased risk of at least 1 exacerbation requiring emergency department visit or hospitalisation or both (OR 0.39, 95% CI 0.19 to 0.78; NNT for an additional beneficial outcome = 27; 963 participants; 7 studies)
  - no effect on % predicted forced expiratory volume in 1 sec or Asthma Control Test scores (MD -0.08, 95% CI -0.70 to 0.54; 713 participants; 3 studies) (Martineau et al. 2016)



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## RCT: Vit D Supplementation & Influenza A

- 2008/2009: 4 month double-blind, placebo-controlled RCT 1200IU/day Vit D<sub>3</sub> supplements, 167 school children in Japan
- Primary outcome: incidence of influenza A (Dx nasopharyngeal swab specimen)
- Results:
  - 10.8% children in Vit D<sub>3</sub> group cf 18.6% children in placebo group contracted Influenza A
  - RR= 0.58 (95% CI: 0.34, 0.99; p= 0.04)
- In children with prev Dx asthma:
  - asthma attacks occurred in 2 children in Vit D<sub>3</sub> group cf 12 children placebo
  - RR: 0.17; 95% CI: 0.04, 0.73; p= 0.006) (Urashima et al. 2010)



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## 5. Zinc & Respiratory Illness: How Can Zinc Help?

- Zinc can inhibit rhinovirus replication & has activity against other respiratory viruses eg, respiratory syncytial VIRUS (Suara et al. 2004)
- Increasing intracellular Zn<sup>2+</sup> concentration with zinc-ionophores like pyrithione (stimulates cellular uptake of Zn) shown to efficiently impair replication of several RNA viruses, incl. poliovirus, influenza virus & several picornaviruses (te Velthuis et al. 2010)
- Combination of Zn<sup>2+</sup> & pyrithione at low concentrations (2 μM Zn<sup>2+</sup> and 2 μM PT) inhibits replication of SARS-coronavirus (SARS-CoV) & equine arteritis virus (EAV) in cell culture (te Velthuis et al. 2010)



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## How Can Zinc Help?

- May also reduce severity of cold symptoms by acting as an astringent on trigeminal nerve (Novick et al. 1996; Godfrey et al. 1992)
- Positively charged, ionic zinc (iZn), (but not bound zinc) strongly astringent, anti-rhinoviral, increases interferon-gamma (IFN- $\gamma$ ) 10-fold, inhibits ICAM-1 & inhibits release of vasoactive ingredients (histamine, leukotrienes) from basophils & mast cells, also anti-viral against other resp viruses incl herpes & respiratory syncytial virus (Eby 2010)



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## iZinc & Common Colds

- A 7-day reduction in duration of common colds was shown by Eby et al. in 1984 using 23 mg zinc gluconate throat lozenges
- Over next 25 years, 14 double-blind, placebo-controlled, RCTs produced widely differing results, approx. 50% showing success & the rest failure
- **WHY?**
- Lozenge iZn fraction varied from 0% to 100% of total lozenge Zn between trials (Zn acetate releases 100% iZn, Zn gluconate releases 72% iZn & other Zn compounds releasing much less or none at physiologic pH 7.4)
- Since only iZn has in vitro benefits, iZn variations hypothesized to have produced the widely varying clinical results
- Analysis: **lozenge iZn & total daily iZn in trials** highly correlated with reductions mean & median duration of common cf. total zinc (iZn plus bound) showed no correlation with changes in duration
- Inferred that iZn is the active ingredient in zinc lozenges for colds, as it is in-vitro against rhinoviruses (Eby 2010)

Zinc lozenges slowly dissolving in the mouth over a 20–30 min period releasing adequate iZn (>18 mg) used each 2 h can shorten common colds by 6–7 days, which is a cure for common colds (Eby 2010).



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## Meta-analysis: Zinc & Common Cold

- 16 therapeutic trials (n=1387) & two preventive trials (n=394)
- RCTs in which oral zinc supplementation was used for  $\geq 5$  consecutive days for treatment or  $\geq 5$  months for prevention included
- Zinc (lozenges or syrup) reduces average duration of common cold in healthy people, when taken within 24 hours of onset of symptoms
- In people taking zinc, cold symptoms are also less likely to persist beyond 7 days of treatment
- Prophylactic zinc supplementation for at least 5 months reduces incidence, school absences & Rx of antibiotics for children with common cold
- Intake of zinc:
  - Assoc with signif. reduction in duration (days) (mean difference (MD) -1.03, 95% CI 1.72 to -0.34) (P = 0.003)
  - Not assoc with severity of common cold symptoms (MD -1.06, 95% CI -2.36 to 0.23, P = 0.11)
  - Proportion symptomatic after 7 days of treatment signif smaller (OR 0.45, 95% CI 0.20 to 1.00, P = 0.05) cf. control
  - Incidence rate ratio (IRR) of developing a cold (IRR 0.64, 95% CI 0.47 to 0.88, P = 0.006), school absence (P = 0.0003) & Rx of antibiotics (P < 0.00001) lower in zinc group (Singh & Das 2015)



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## Meta-analysis: Zinc & Common Cold

- 17 RCTs (2121 participants)
- Those receiving zinc shorter duration of cold symptoms (mean difference -1.65 days, 95% CI -2.50 to -0.81) cf placebo
  - Adults: Zn shortened duration of cold symptoms cf placebo (mean difference -2.63, 95% CI -3.69 to -1.58)
  - Children: no significant diff (mean difference -0.26, 95% CI -0.78 to 0.25)
- No signif effect on severity of cold symptoms (Science et al. 2012)



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## 6. Recommendations for Supplementation: Prevention of Colds & Flu

- Supplementation with Vitamin C: 1000mg-2000mg daily
- Supplementation with Vitamin D: 1000-4000 IU daily (test for Vit D levels)
- Supplementation with Zinc: 30mg



## Recommendations for Supplementation: Treatment of Cold & Flu (no pneumonia)

- Without progression to pneumonia, increase dosages of Vit C, D & Zn
  - Supplementation with Vitamin C: up to 10,000 mg daily (spread out over course of day, bowel tolerance will vary)
  - Supplementation with Vitamin D: 4,000-10,000 IU daily
  - Supplementation with Zinc: 60mg daily (for 2 weeks max.)

## Recommendations for Treatment: Pneumonia, ALI and ARDS

- Intravenous high-dose Vitamin C is essential
- Dosages can range from: 50g to 200g (or more if pt. is critical)
- Chinese hospitals have been using dosages of: 50g+
- Need to test for G6PD-deficiency



## 7. Key Messages

- COVID-19 pandemic
- Those with compromised immune systems & pre-existing diseases are more at risk
- Key govt messages about hygiene & transmission vital to heed
- Keeping immune system strong = important strategy in preventing colds, flus & COVID-19 & reducing severity of infection
- Key Supplements for prevention: Vitamin C, Vitamin D & Zinc
- Key vitamin to treat COVID-19 ARDS: high dose IV Vit C

## How to Learn More

The **Australasian College of Nutritional and Environmental Medicine (ACNEM)** provides education in nutritional and environmental medicine for healthcare practitioners

Visit ACNEM at [www.acnem.org](http://www.acnem.org)



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