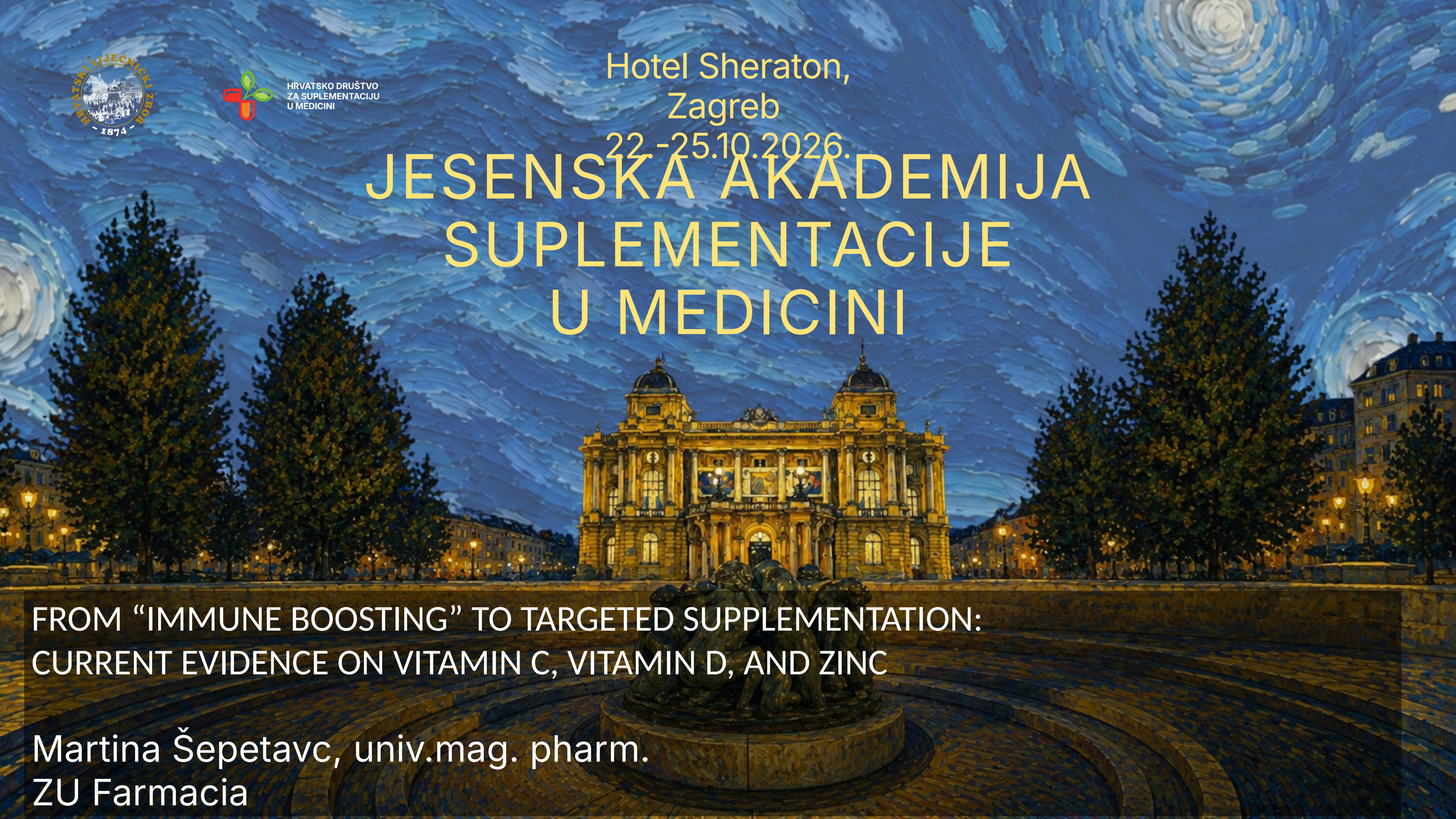
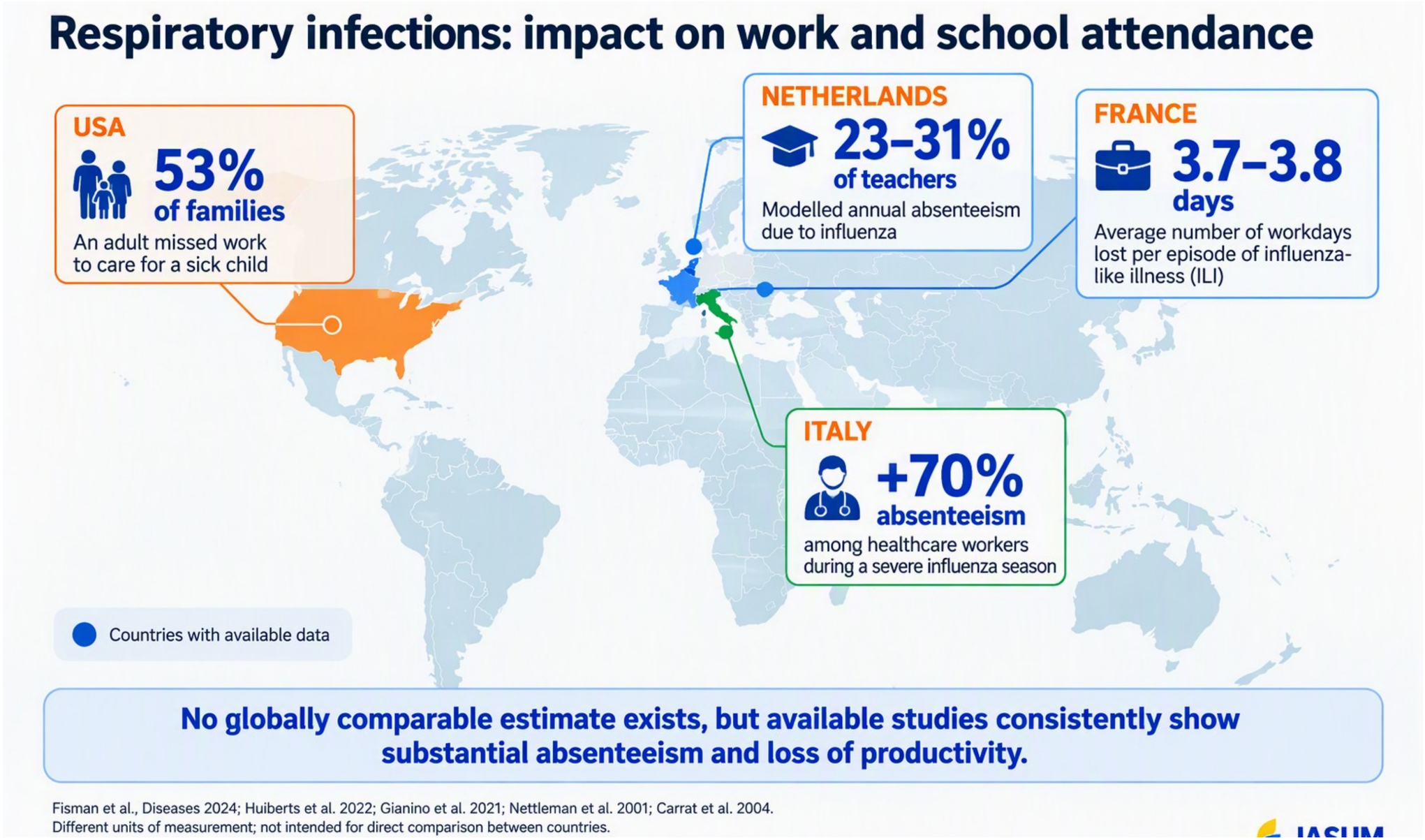


FROM “IMMUNE BOOSTING” TO TARGETED SUPPLEMENTATION: CURRENT EVIDENCE ON VITAMIN C, VITAMIN D, AND ZINC

Martina Šepetavc, univ.mag. pharm.
ZU Farmacia




Respiratory infections: impact on work and school attendance
USA
53%
of families
An adult missed work to care for a sick child
NETHERLANDS
23–31%
of teachers
Modelled annual absenteeism due to influenza
FRANCE
3.7–3.8
days
Average number of workdays lost per episode of influenza-like illness (ILI)
ITALY
+70%
absenteeism
among healthcare workers during a severe influenza season
Countries with available data
No globally comparable estimate exists, but available studies consistently show substantial absenteeism and loss of productivity.
Fisman et al., Diseases 2024; Huiberts et al. 2022; Gianino et al. 2021; Nettleman et al. 2001; Carrat et al. 2004.
Different units of measurement; not intended for direct comparison between countries.

Hidden hunger in Europe: well fed yet undernourished

European Commission

EU-funded researchers are exploring the issue of hidden hunger in Europe to understand why people who have enough food to eat may not be getting sufficient micronutrients to maintain good health.

The research kicked off in January 2024 and will conclude in December 2027. It brings together experts from 10 EU countries, the UK and Switzerland, as well as the International Agency for Research on Cancer, the European Food Information Council and the European Public Health Alliance.

Certain parts of the population are more likely to suffer from deficiencies – the elderly, growing children and pregnant women, for instance. Altogether, they estimate that as many as 70% of the population are at risk of micronutrient deficiency.

https://projects.research-and-innovation.ec.europa.eu/en/horizon-magazine/hidden-hunger-europe-well-fed-yet-undernourished

From “immune boosting” to targeted supplementation

TRADITIONAL MESSAGE

vitamin C
“boosts immunity”

vitamin D
“prevents infections”

zinc
“treats the common cold”

MODERN SCIENTIFIC FRAMEWORK

An adequate nutritional status
is a prerequisite for optimal immune function.

Deficiency may increase
the risk of infections and adverse outcomes.

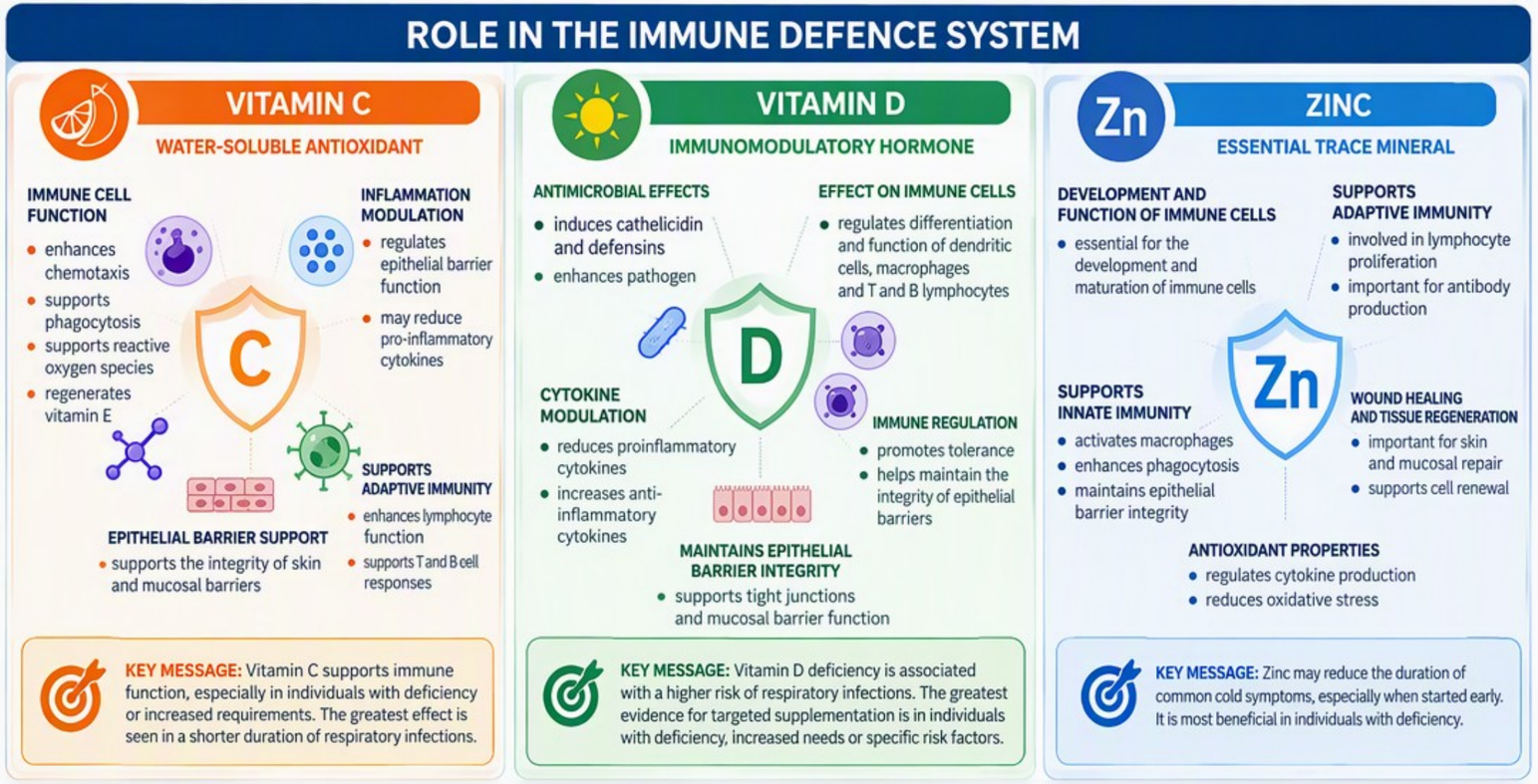
Correction of deficiency
has biological and clinical justification.

Routine supplementation in healthy individuals
shows limited and inconsistent benefit.

The key question is no longer “what boosts immunity?”, but “who has a deficiency, increased needs or risk factors?”

Calder 2020; Maggini i sur. 2018; Gombart i sur. 2020; Jolliffe i sur. 2021

Why are vitamin C, vitamin D and zinc important?



KEY POINTS

- **Function** in innate and adaptive immunity
- **Integrity** of skin and mucosal barriers
- **Regulation** of cytokines and inflammatory response
- **Protection** against oxidative stress

A biological role does not automatically mean that supplementation prevents or treats respiratory infections.

Clinical benefit depends on baseline status, age, comorbidities, regimen of use and risk of deficiency.

Maggini i sur. 2018; Gombart i sur. 2020; Carr & Maggini 2017; Gammoh & Rink 2017

Vitamin C, vitamin D and zinc: an evidence overview

NUTRIENT	PREVENTION	USE DURING INFECTION	WHO MAY HAVE THE GREATEST BENEFIT
VITAMIN C	Does not reduce the incidence of the common cold in the general population.	Regular use may shorten duration of symptoms; insufficient evidence for the prevention or treatment of pneumonia.	Individuals with deficiency, smokers, chronic diseases, intensive physical stress (e.g. endurance athletes).
VITAMIN D	No overall universal effect; a more favourable signal with daily supplementation.	Insufficient evidence for routine treatment of acute respiratory infections.	Individuals with deficiency, older adults, low sun exposure, chronic diseases.
ZINC	Use mainly studied in populations with deficiency or increased risk.	Greatest potential benefit when started within 24 hours of the onset of common cold symptoms.	Individuals with deficiency, older adults, malabsorption, selected paediatric populations.

Sažetak prema referencama 7–15, 18, 20, 24 i 25 u radu za MEDICUS

Vitamin C: biological role, status and risk groups

IMMUNOLOGICAL ROLE

- **Antioxidant** protection during inflammation
- **Migration and** function of **phagocytes**
- **Differentiation** and proliferation of B and T **lymphocytes**
- **Collagen synthesis** and maintenance of epithelial barrier integrity

RISK GROUPS FOR DEFICIENCY

- **Older** adults
- **Smokers**
- **Chronic diseases**
- **Low intake** of fruits and vegetables
- **Increased requirements** during infections

PRACTICAL GUIDANCE

- **Prioritise dietary sources** (fruits and vegetables)
- **Supplement** in case of proven or likely deficiency
- **Do not recommend** high doses routinely for the prevention of infections
- **Distinguish** a health claim from a clinically proven benefit

Rowe & Carr 2020; Carr & Maggini 2017

Vitamin C and respiratory infections: what do the evidence show?

ELSEVIER

Current Reviews in Clinical and Experimental Pharmacology

Volume 17, Issue 3, 2022, Pages 205–215



Meta-Analysis

Effect of Vitamin C Supplements on Respiratory Tract Infections: A Systematic Review and Meta-Analysis

Tahmina Afrose Keya [1], Anthony Leela [1], Kevin Fernandez [1], Nasrin Habib [2], Mumunur Rashid [3]

Show more

+ Affiliations

PMID: 34967304 DOI: 10.2174/2772432817666211230100723

Regular supplementation does not reduce the incidence of the common cold in the general population.

8 % Shorter duration of the common cold **in adults**

14 % Shorter duration of the common cold **in children**

≈50 % Lower incidence in marathon runners, skiers and military personnel **during subarctic training**

For pneumonia: there is insufficient high-quality evidence for routine prevention or treatment.

Hemilä & Chalker 2013; Padhani i sur. 2021

Vitamin C: dose, safety and counselling

DOSE / SITUATION	CLINICAL SIGNIFICANCE	PHARMACIST'S RECOMMENDATION
95 mg (women) / 110 mg (men)	EFSA population reference intake for healthy adults	Diet remains the primary source.
200 mg – 2 g/day	Dose range often used in studies on respiratory infections	Do not equate the investigated dose with routine requirements.
>2 g/day	Nausea, abdominal discomfort and diarrhoea	Warn about potential gastrointestinal adverse effects.
History of oxalate kidney stones	Possible increased urinary oxalate excretion with long-term high doses	Exercise particular caution and avoid non-individualised long-term supplementation.

EFSA NDA Panel 2013; NIH ODS; Farkouh i sur. 2026

Vitamin C: how to translate the evidence into a recommendation?

1. PREVENTION

- General population: **no reduction in the incidence** of the common cold.
- Exception: individuals exposed to **short-term intense physical stress** (e.g. endurance athletes, military personnel).
- **Do not recommend** routine high-dose supplementation for prevention.

2. COURSE OF THE COMMON COLD

- Regular use may **shorten the duration** of symptoms.
- The effect is **modest** on average and **clinically small**.
- Starting supplementation only after symptom onset is **not as well supported** by evidence.

3. DECISION IN PRACTICE

- **Assess** diet, smoking, chronic diseases and increased requirements.
- **Prioritise dietary sources** (fruits and vegetables).
- In the case of probable or proven deficiency, **choose a reasonable dose and duration**.
- **Check** for a history of kidney stones and gastrointestinal tolerability.

Key message: vitamin C **supports** normal immune function, but supplementation is not a universal protection against infections.

Hemilä & Chalker 2013; Rowe & Carr 2020; Carr & Maggini 2017; Padhani i sur. 2021

Vitamin D: immunological role and data from Croatia

IMMUNOLOGICAL ROLE

- Stimulation of cathelicidin and defensins
- Modulation of macrophage activity
- Balance of pro-inflammatory and anti-inflammatory cytokines
- Maintenance of the integrity of epithelial barriers in the respiratory tract

CROATIA, n = 829

7.1 % ≥75 nmol/L

49.2 % 50–75 nmol/L

43.7 % <50 nmol/L

More than 90 % of participants did not reach ≥75 nmol/L.

RISK FACTORS FOR DEFICIENCY

- Winter months and limited sun exposure
- Older age, obesity, pregnancy
- Malabsorption, liver and kidney disease
- Glucocorticoids, phenytoin, carbamazepine and ketoconazole

Kelemen i sur. 2025; hrvatske smjernice 2016; Demay i sur. 2024

JOURNAL ARTICLE CORRECTED PROOF

Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline FREE

Marie B Demay ✉, Anastassios G Pittas, Daniel D Bikle, Dima L Diab, Mairead E Kiely, Marise Lazaretti-Castro, Paul Lips, Deborah M Mitchell, M Hassan Murad, Shelley Powers ... Show more

Author Notes

The Journal of Clinical Endocrinology & Metabolism, dgae290, https://doi.org/10.1210/clinem/dgae290

Published: 03 June 2024 **Article history** ▾

Conclusion

The panel suggests empiric vitamin D for those aged 1 to 18 years and adults over 75 years of age, those who are pregnant, and those with high-risk prediabetes. Due to the scarcity of natural food sources rich in vitamin D, empiric supplementation can be achieved through a combination of fortified foods and supplements that contain vitamin D. Based on the absence of supportive clinical trial evidence, the panel suggests against routine 25(OH)D testing in the absence of established indications. These recommendations are not meant to replace the current DRIs for vitamin D, nor do they apply to people with established indications for vitamin D treatment or 25(OH)D testing. Further research is needed to determine optimal 25(OH)D levels for specific health benefits.

Ages 1-18	Ages 19-49	Ages 50-74	Ages ≥75	Pregnancy	Prediabetes
Empiric vitamin D supplementation* To prevent nutritional rickets and because of the potential to lower the risk of respiratory tract infections.	**No empiric vitamin D supplementation*** Follow the Institute of Medicine Recommended Daily Allowance.		**Empiric vitamin D supplementation*** Because of the potential to lower the risk of mortality.	**Empiric vitamin D supplementation*** Because of the potential to lower the risk of preeclampsia, intrauterine mortality, preterm birth, small for gestational age birth and neonatal mortality.	**Empiric vitamin D supplementation*** Because of the potential to lower the risk of progression to diabetes.

The panel assumed that all should follow the Recommended Dietary Reference Intakes (DRI) established by the US Institute of Medicine (currently the National Academy of Medicine). The Recommended Daily Allowance (RDA) in the DRI is 600 IU (15 μg) for persons aged 1-70 years and 800 IU (20 μg) for persons older than 70 years. The RDA established by the the Institute of Medicine and the American College of Obstetricians and Gynecologists (ACOG) is 600 IU (15 μg) during pregnancy.

* **Empiric vitamin D supplementation** refers to vitamin D (cholecalciferol [D_3] or ergocalciferol [D_2]) intake (usually in pill or drop form) that (a) exceeds the DRIs and (b) is implemented without testing for 25-hydroxyvitamin D. Vitamin D doses in the included clinical trials varied considerably (see technical remarks under recommendations); hence, optimal doses remain unclear.

For people older than 50 years for whom vitamin D treatment is indicated, the panel suggests supplementation via daily administration of vitamin D, rather than intermittent high doses.

The panel suggests against routine 25-hydroxyvitamin D testing for generally healthy individuals who do not otherwise have established indications for 25-hydroxyvitamin D testing (e.g., hypocalcemia). The panel did not specifically address whether and how those who present with low levels of 25-hydroxyvitamin D should be evaluated and/or treated.

* Importantly, this guideline does not address individuals with underlying conditions that substantially alter vitamin D physiology, including various conditions associated with decreased absorption (e.g., short gut, gastric bypass, inflammatory bowel disease), increased catabolism/decreased activation (e.g., some medications), and increased renal losses (e.g., nephrotic syndrome). In addition, this guideline does not address persons known to be at high risk for fractures.

Vitamin D and acute respiratory infections:
the regimen changes the interpretation

nutrients MDPI

Meta-Analysis

Optimal methods of vitamin D supplementation to prevent acute respiratory infections: a systematic review, dose–response and pairwise meta-analysis of randomized controlled trials

Chih-Hung Wang [1,2], Lorenzo Porta [3,4], Ting-Kai Yang [2], Yu-Hsiang Wang [5], Tsung-Hung Wu [5], Frank Qian [6], Yin-Yi Han [7], Wang-Huei Sheng [5], Shyr-Chyr Chen [1,2], Chien-Chang Lee [8,9,10], Shan-Chwen Chang [11]

Nutrients. 2024, 14(23), 92. https://doi.org/10.1186/s12937-024-00990-w

43 RCTs

> 49,000 participants

Overall analysis: no statistically significant benefit

MORE FAVOURABLE SIGNAL IN SUBGROUPS

DAILY REGIMEN
400–1200 IU/day

- More favourable results with daily dosing
- In studies shorter than 4 months
- During autumn, winter and spring (outside summer)

SEASON
autumn, winter, spring

- Greater preventive effect observed outside summer months

DOSE RANGE
400–1200 IU/day

- Optimal range in the dose–response analysis

The results of this meta-analysis support a small preventive effect of daily vitamin D supplementation (400–1200 IU), particularly outside the summer season; this finding needs to be confirmed in future trials.

Vitamin D is not a treatment for confirmed acute respiratory infection, but it may have a small preventive effect in specific conditions.

Wang et al. *Nutrients*. 2024;14:92. · Jolliffe et al. *Lancet Diabetes Endocrinol*. 2021;9;733–746.

JASUM

Vitamin D: who, how and with what precautions?

EMPIRICAL SUPPLEMENTATION ACCORDING TO 2024 GUIDELINES

- Children and adolescents 1–18 years
- Pregnant women
- Adults aged ≥75 years
- Individuals with high-risk prediabetes

HEALTHY ADULTS <75 YEARS

- No routine doses above the recommended daily intake
- No routine measurement of 25(OH)D for disease prevention
- Target concentrations for disease prevention are not defined

PRACTICAL PRECAUTIONS

- Very high bolus doses may be associated with falls and fractures in older adults
- Adjust the formulation and dose to individual indications and risk factors
- Consider comorbidities and medications that affect vitamin D metabolism

Demay i sur. 2024; hrvatske smjernice 2016

Vitamin D: how to link status, regimen and goal of use?

STATUS

- Vitamin D status is generally **low in the Croatian population**, based on clinical practice data.
- Risk increases with **limited sun exposure**, older age, obesity, malabsorption and certain medications.
- **Measurement of 25(OH)D** is recommended in individuals with a clinical indication or increased risk.

REGIMEN

- **Daily administration** shows a more favourable signal than intermittent high-dose boluses.
- In a meta-analysis of respiratory infections, the optimal range was **400–1200 IU/day**.
- **Very high bolus doses** are not a routine strategy for disease prevention.

GOAL OF USE

- **Prevent or correct deficiency** in at-risk individuals.
- **Do not expect universal prevention** of respiratory infections.
- **Differentiate** between disease prevention in healthy individuals and treatment of a confirmed deficiency.

Key message: The decision to use vitamin D should be based on the individual clinical context, not a single universal target value.

Demay i sur. 2024; Wang i sur. 2024; Kelemen i sur. 2025; hrvatske smjernice 2016

Zinc: biological role, status and at-risk groups

IMMUNOLOGICAL ROLE

- Maturation of **T lymphocytes** in the thymus
- Proliferation of **B lymphocytes**
- Activation of **natural killer (NK)** cells
- Function of **macrophages and neutrophils**
- Maintenance of the integrity of the **skin and mucosal barriers**

RISK OF DEFICIENCY

- Malnutrition and malabsorption
- Chronic gastrointestinal diseases
- Chronic kidney disease
- Older age
- ACE inhibitors and diuretics may increase urinary zinc loss

KEY MESSAGE

An adequate zinc status and prevention of deficiency

≠

universal treatment of established infections

Gammoh & Rink 2017; Li i sur. 2022; Bahadoran & Hosseinpanah 2026

Zinc in the early phase of the common cold: formulation, timing and dose matter

Open access Meta-analysis

BMJ Open Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials

Jennifer Hunter[1], Susan Arentz[2], Joshua Goldenberg[3], Guoyan Yang[2], Jennifer Beardsley[4], Stephen P Myers[2,5], Dominik Mertz[6], Stephen Leeder[7]

ABSTRACT

Conclusions Zinc may be effective in reducing the duration of symptoms of the common cold when started within 24 hours of symptom onset, but the certainty of evidence is low. Higher doses (>75 mg/day) have been used in most positive trials, with no clear additional benefit above 100 mg/day.

BMJ Open. 2021 Nov 2;11(11):e047474. doi: 10.1136/bmjopen-2020-047474.

≤24 h
Start within 24 hours
of symptom onset

80–92 mg/day
Elemental zinc
in most positive trials

LOZENGES
Zinc acetate or gluconate
(sublingual)

SHORT TERM
During the first days
of the common cold

The evidence is more robust for the common cold than for pneumonia or more severe infections.

Additional benefit above 100 mg/day has not been confirmed.

Hemilä 2017; Hemilä & Chalker 2015; Hunter i sur. 2021

Zinc: safety, interactions and limits of evidence

SITUATION	RISK / LIMITATION	PRACTICAL RECOMMENDATION
Chronic total intake	European upper limit 25 mg/day	Do not use short-term high doses (e.g. 80–92 mg/day) continuously
Long-term high doses	Risk of copper deficiency, impaired iron metabolism and anaemia	Check the dose and duration of all dietary supplements
Tetracyclines and fluoroquinolones	Chelation and reduced antibiotic absorption	Take zinc at least 2 hours before or 4–6 hours after the antibiotic
Intranasal zinc	Risk of permanent or long-term loss of sense of smell (anosmia)	Not recommended
Pneumonia	Inconsistent results and insufficient evidence	Do not recommend routine use as a therapy

Scientific Committee on Food 2003; Shane-McWhorter 2025; WHO 2023

Zinc: how to link preventive and therapeutic use?

ADEQUATE STATUS

- Important for the function of T lymphocytes, NK cells, macrophages and mucosal barriers
- The greatest benefit from supplementation is expected in case of deficiency or increased risk
- Assess dietary intake, malabsorption, kidney disease, age and medications

EARLY COMMON COLD

- Start within 24 hours of symptom onset
- Strongest evidence for lozenges with zinc acetate or gluconate
- In positive trials most commonly 80–92 mg of elemental zinc per day, short-term
- A later start shows a smaller effect

LIMITS OF EVIDENCE

- The evidence for a meaningful effect on the common cold is moderate
- For pneumonia and severe infections the results are not sufficiently reliable
- Short-term therapeutic doses are not appropriate for long-term continuous supplementation

Key message: when recommending zinc, clearly define the goal, pharmaceutical form, timing of initiation, dose and duration.

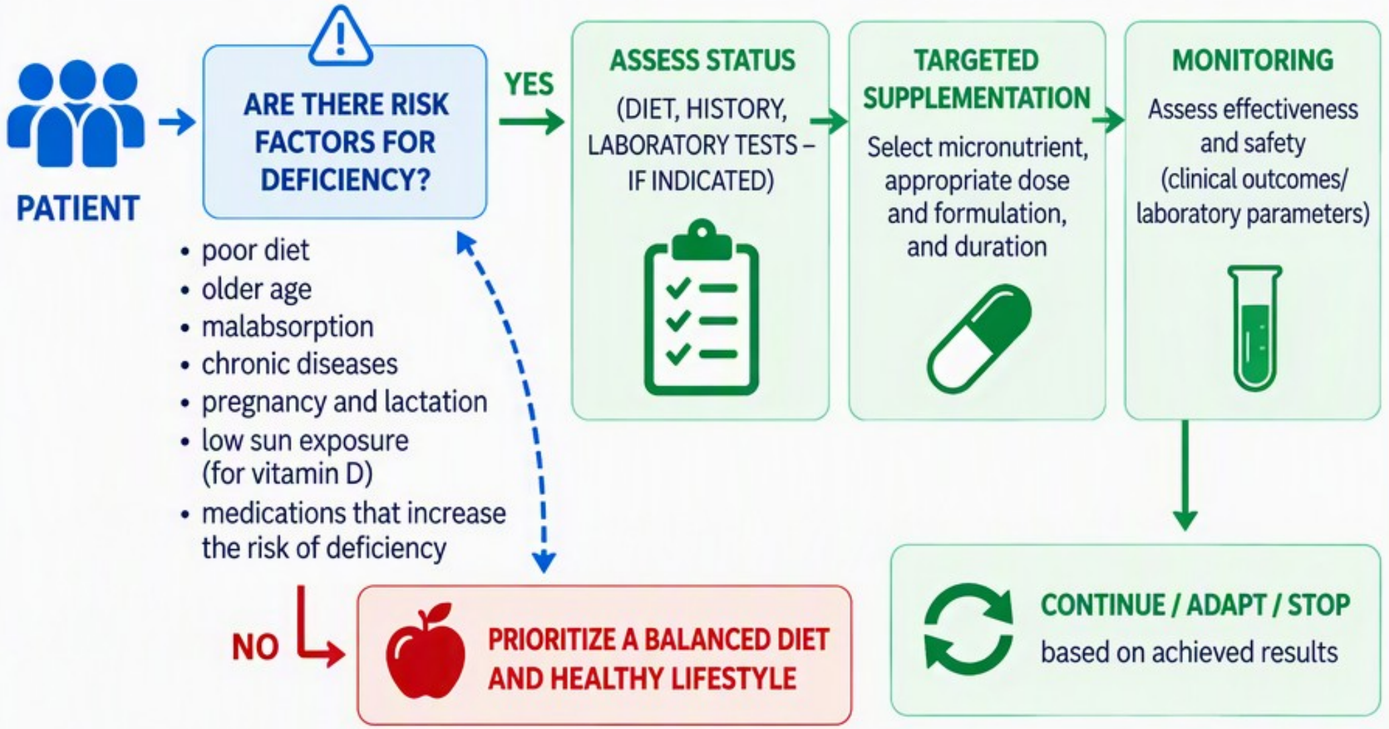
Hemilä 2017; Hemilä & Chalker 2015; Hunter i sur. 2021; Imdad i sur. 2023; WHO 2023

Summary of evidence for vitamin C, vitamin D and zinc

Nutrient	Immunological role	Evidence for prevention of respiratory infections	Evidence for treatment	Populations most likely to benefit	Practical notes
C Vitamin C 	• Antioxidant protection • Function of neutrophils and lymphocytes • Maintenance of skin and mucosal barriers	• Regular supplementation **does not reduce the incidence** of the common cold in the general population. • Reduced incidence in individuals exposed to **short-term intensive physical stress.**	• Regular use shortens the duration of the common cold by **~8%** in adults and **~14%** in children.	• Individuals with deficiency • Smokers • Chronic diseases • Individuals exposed to intensive physical stress	• **Recommended** daily intake (EFSA): **95 mg (women), 110 mg (men)** • **Doses used in studies: 200 mg – 2 g/day** • **>2 g/day:** gastrointestinal adverse effects • Caution in individuals with a history of calcium oxalate kidney stones
D Vitamin D 	• Regulation of innate and adaptive immunity • Stimulation of cathelicidin and defensins • Promotion of antimicrobial peptide synthesis • Modulation of cytokine response	• No significant benefit in overall analyses. • Meta-analysis (49,320 participants, 43 RCTs) shows a small preventive effect with **daily dosing 400–1200 IU/day,** especially outside summer and in shorter studies (<4 months).	• Insufficient evidence for routine use in the treatment of acute respiratory infections.	• Individuals with deficiency • Older adults • Pregnant women • Individuals with limited sun exposure • Individuals with obesity or malabsorption • Chronic diseases	• Most evidence for **400–1200 IU/day** (daily regimen) • 25(OH)D testing: not recommended routinely in healthy individuals • Endocrine Society guidelines (2024): empiric supplementation for children 1–18 years, pregnant women, adults ≥75 years and individuals with high-risk
Zn Zinc 	• Function of T cells, NK cells and macrophages • Maintenance of mucosal barriers • Regulation of inflammatory response	• May be beneficial in populations at increased risk of zinc deficiency.	• Greatest benefit when started **within 24 hours** of symptom onset. • High-dose lozenges (>75 mg/day, commonly **80–92 mg/day)** can shorten the duration of the common cold. • Insufficient evidence for pneumonia.	• Children with recurrent respiratory infections • Individuals with deficiency • Older adults • Individuals with malabsorption • Individuals using ACE inhibitors or diuretics (increased urinary zinc loss)	• Lozenges with zinc acetate or gluconate • **Short-term** use only during the first days of a cold • Do not exceed **100 mg/day** (elemental zinc) for cold treatment • **European** upper limit for chronic total intake: 25 mg/day (adults) • Take zinc ≥2 **hours** before or 4–6 hours after tetracyclines or fluoroquinolones • Intranasal zinc: not recommended (risk of anosmia)

Targeted supplementation in clinical and community pharmacy practice

WHEN TO CONSIDER SUPPLEMENTATION?

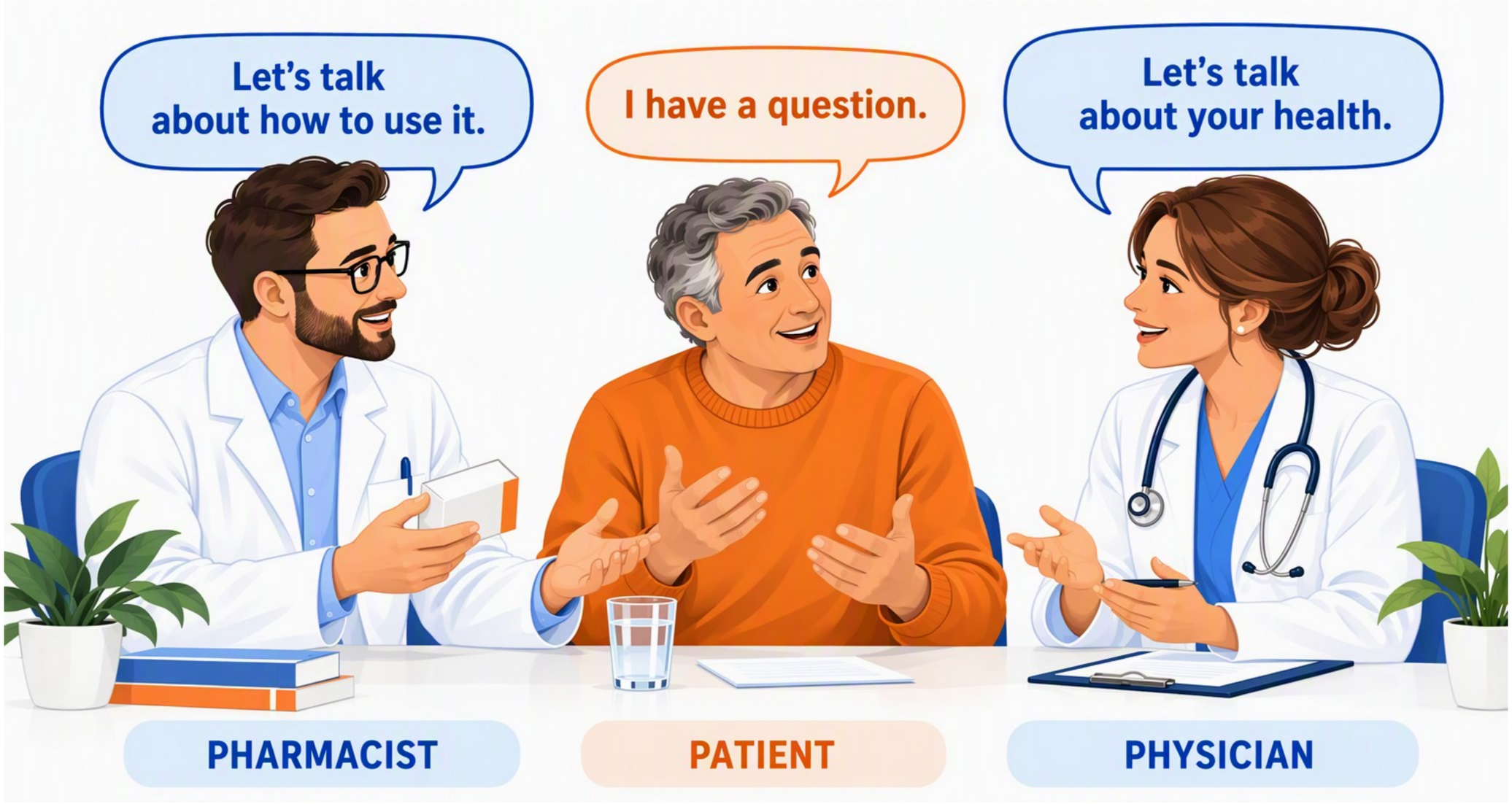


Micronutrient supplementation is not a substitute for a balanced diet.
The greatest benefit is seen in individuals with a confirmed deficiency, increased needs, or specific risk factors for lower micronutrient status.

ROLE OF PHYSICIANS AND PHARMACISTS

- **Identify risk factors** and symptoms suggestive of deficiency
- **Assess diet,** age, lifestyle, comorbidities, BMI and current pharmacotherapy
- **Differentiate** correction of deficiency from attempts to treat acute infection
- **Select** an appropriate product, formulation, dose and duration
- **Check for** duplicate supplementation, interactions and potential adverse effects
- **Refer to a physician** when additional diagnostics or targeted treatment is needed


A PARADIGM SHIFT
From “boosting immunity”
to status assessment and
targeted supplementation
IDENTIFY RISK · ADDRESS DEFICIENCY · COUNSEL SAFELY


Let's talk about how to use it.
I have a question.
Let's talk about your health.
PHARMACIST
PATIENT
PHYSICIAN