I-PREVENT℠

COVID, FLU AND RSV PROTECTION

A guide to preventing COVID-19, influenza and Respiratory Syncytial Virus (RSV)

December 2024

Updates:
- New evidence in use of Listerine™ for short-term use only
- Caution on potential tooth staining from mouthwash (2/2024)

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Disclaimer

The information in this document is our recommended approach to preventing COVID-19, influenza, and Respiratory Syncytial Virus (RSV) infections in adults. Patients should always consult with a trusted healthcare provider before starting any medical treatment as this protocol may need to be personalized based on the patient's age, demographics, and co-morbidities.

As this is a highly dynamic topic, we will update these guidelines as new information emerges. Please ensure you are using the latest version of this protocol.

Overview of I-PREVENT

The pattern of infection with SARS-Co-V2, influenza, and RSV has evolved over time. While influenza and RSV infections were uncommon during 2020 and 2021, (1-5) a dramatic increase in influenza and RSV infections was documented in the fall and early winter of 2022. The reason for this change in disease pattern is controversial, but likely related to the lifting of lockdowns and the widespread COVID-19 vaccination program. We have therefore adapted the I-PREVENT protocol to include prevention against influenza and RSV infection. The interventions we recommend are likely to reduce the risk and severity of infection with COVID-19, influenza, and RSV infections as well as the common cold. It should be noted that the medications included in I-PREVENT are inexpensive, safe, and widely available.

The I-PREVENT protocol includes a **pre-exposure (long-term)** protocol as well as a **post-exposure (acute, short-term)** protocol.

- **The pre-exposure prevention protocol** is especially recommended for healthcare workers, as well as high-risk individuals (such as those over 60 years old) or those with comorbidities.
- **The post-exposure protocol** is recommended in asymptomatic household members of a patient with proven COVID, influenza, or RSV infection, as well as asymptomatic individuals who have had contact with an individual and or individuals (large crowd setting) who likely had COVID-19, influenza, or RSV infection.
- **At the onset of flu-like symptoms** please refer to the I-CARE: Early COVID Treatment or I-CARE: RSV and Flu Treatment Protocols.

Pre-Exposure (Long-Term) Prevention

How to prevent infection before you've been exposed

Antiseptic antimicrobial mouthwash

Antiseptic-antimicrobial mouthwashes that include chlorhexidine, povidone-iodine, or cetylpyridinium chloride or the combination of eucalyptus, menthol, and thymol (Listerine™) have been shown to inhibit the replication of many upper respiratory tract viral pathogens and to reduce viral load. [6-13]

- **Dosing and administration**
  Gargle twice daily with a mouthwash that includes chlorhexidine, povidone-iodine, or cetylpyridinium chloride or the combination of eucalyptus, menthol, and thymol. Do not swallow.

  This practice will likely reduce the amount of virus in the upper airways, thereby reducing the risk of symptomatic disease and reducing disease severity.

- **Mechanisms**
  A mouthwash containing cetylpyridinium chloride (CPC) has broad antimicrobial properties and has been shown to be effective in controlling gingivitis and gingival plaque. (6-8)

  An in-vitro study demonstrated that CPC was highly virucidal against a human coronavirus. (9) In a primary prophylaxis study, a povidone-iodine throat spray administered three times daily proved to be highly effective in reducing the risk of laboratory confirmed SARS-CoV-2 infection.

  Inhaled steam supplemented with antimicrobial essential oils (e.g., VapoRub™ inhalations) once a day has also been demonstrated to have virucidal activity. (10)

  Antimicrobial essential oils include lavender oil, thyme oil, peppermint oil, cinnamon oil, eucalyptus oil and sage oil. (10-14)

- **Cautions and contraindications**
  Some mouthwashes may contribute to temporary tooth staining in certain individuals. Discontinue use and try a different product if this problem arises. Please note that chronic use of Listerine™ increases fusobacterium in the oral and gut microbiome. (15, 16) Fusobacterium is associated with many cancers including colorectal, breast, oral, etc. (17, 18) We there suggest that Listerine™ be used for short term use.

Vitamin D

Vitamin D deficiency is common in the Middle East and some countries in Asia, Europe, and North America. (19, 20) Reduced sun exposure, common sunscreen use, increased body mass index (BMI), less physical activity, age, skin pigmentation, and poor socioeconomic status predict lower serum 25(OH)D concentrations. Vitamin D insufficiency has been associated with an increased risk of COVID-19 infection and dying from the disease. (21-25)

- **Dosing and administration**
  Dosing recommendations varies; an optimal target is greater than 50 ng/ml. (24) It is best to include both Vitamin K2 (Menaquinone [MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of Vitamin D > 8000 IU/day are taken. (26, 27)

  It may take many months or even years to achieve optimal levels in patients with low Vitamin D levels (<12 ng/ml) taking the standard recommended dose of 5,000 IU/day. It is therefore important

that the optimal regimen for Vitamin D supplementation for protection against viral upper respiratory tract infection be based on the baseline Vitamin D level.

Since the highest dose of commercially available Vitamin D3 is 50,000 IU capsules, and due to its affordability (low cost) and better gastrointestinal absorption, we recommend using 50,000 IU D3 capsules for non-urgent outpatients and community setups. Together, a number of these capsules can be taken as a bolus dose [i.e., single upfront doses such as 100,000 to 400,000 IU]. However, the liver has a limited 25-hydroxylate capacity to convert Vitamin D to 25(OH)D: thus, taking 50,000 IU capsules over a few days provides better bioavailability.

Table 2 presents a safe and practical treatment schedule for raising blood 25(OH)D concentrations and tissue storage without adverse effects in non-urgent situations (modified from SJ Wimalawansa with permission). (28) The dosing schedule illustrated in Table 3 should be used when recent serum 25(OH)D concentration levels are unavailable. (28)

- **Mechanisms**
  Vitamin D receptors are present on immune cells, with this vitamin playing a critical role in both innate and adaptive host immunity. (29, 30) Vitamin D has numerous immunological properties that play a vital role in protecting against and limiting the severity of COVID-19 and influenza. (31)

Vitamin C

Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties. (32-37) The effects of Vitamin C on the course of upper respiratory tract infections have long been recognized. (38)

- **Dosing and administration**
  500 mg twice daily.

- **Mechanisms**
  Vitamin C increases synthesis of type I interferons (hosts primary anti-viral mechanism) and the innate antiviral response mediated by RIG-I-mediated signal transduction pathways. (39) The non-absorbed fraction of Vitamin C enhances the proliferation of *Bifidobacterium* in the gut microbiome.

Zinc

Zinc is essential for innate and adaptive immunity, with zinc deficiency being a major risk factor for influenza and RSV infection. (40-43)

- **Dosing and administration**
  20-50 mg/day. Commercial zinc supplements are commonly formulated as zinc oxide or salts with acetate, gluconate, and sulfate.

- **Mechanisms**
  Zinc has demonstrated the ability to inhibit the replication of influenza virus. (44) In addition, zinc inhibits RNA-dependent RNA polymerase in vitro against SARS-CoV-2 virus. (45) Zinc reduces RSV burden in the lungs. (43)

- **Cautions and contraindications**
  Due to competitive binding with the same gut transporter, *prolonged* high-dose zinc (> 50mg day) should be avoided, as this is associated with copper deficiency. (46)

Melatonin

- **Dosing and administration**
  1-6 mg nightly (slow/extended release). Begin with 1 mg and increase as tolerated to 6 mg at night. Causes drowsiness. (47-55).

  Melatonin undergoes significant first pass metabolism in the liver with marked individual variation; this explains the wide dosing requirement.

- **Mechanisms**
  Melatonin has anti-inflammatory, antioxidant, immunomodulating, and metabolic effects that are likely important in the mitigation of COVID-19 influenza and RSV infections. [50-52]

- **Cautions and contraindications**
  Some patients are intolerant to melatonin, having very disturbing and vivid dreams; in these patients, it may be best to start with a 0.3 mg slow-release tablet and increase slowly, as tolerated.

Elderberry

Black elderberry (Sambucus nigra) has traditionally been used to treat cold and flu symptoms. Elderberries contain a great variety of flavones, isoflavones, flavanols, anthocyanins, phenolic acids, lectins, and many vitamins. The antiviral properties of elderberries include activity against coronaviruses and influenza viruses (56-60) Elderberries have been shown to reduce the duration and severity of symptoms in patients with the "common cold." (61)

- **Dosing and administration**
  Take elderberry syrups, gummies, or supplements to prevent viral upper respiratory tract infections **during periods of high transmission** of COVID-19, influenza, and RSV. Follow manufacturer's dosing recommendations. A triple combination containing elderberry, Vitamin C, and zinc may be a convenient approach.

  Elderberry fruit extracts have most often been used by adults in doses up to 1200 mg daily taken orally for 2 weeks. Elderberry is available in many different types of products, including syrups, tablets, gummies, and mouth rinses. Elderberry supplements, gummies, and syrup may be obtained from your local pharmacy (e.g. NatureMade Elderberry with Vitamin C and Zinc) or from the following suppliers/manufacturers (https://thepowerofelderberries.com/, https://www.NorthernElderberry.com, https://www.puritan.com/, https://www.amazon.com/ https://sambucolusa.com/, https://gobblemountain.com/).

  Elderberries have not been reported to have drug-food interactions. (62) Elderberries do not contain phytochemicals known to increase the risk of miscarriage, cause birth defects, change hormonal function, or reduce breast milk supply. However, animal and human studies are lacking, and therefore there is insufficient data to recommend this nutraceutical during pregnancy or breastfeeding. (63)

- **Mechanisms**
  The active chemicals include anthocyanins, primarily cyanidin 3-glucoside (C3G) and cyanidin 3-sambubioside, which have been shown to have antiviral, antibacterial, antidiabetic, antitumor, antioxidant, antidepressant, and immune-boosting properties. (56, 57) It should be noted that C3G interacts with the gut microbiome and the intestinal mucosal immune system to maintain gut health. (64)

- **Cautions and contraindications**
  Don't consume green, unripe, uncooked elderberries or the stem and leaves of this plant as they contain toxins (cyanide) and can be poisonous.

  A number of authors have suggested that elderberries should be used with caution in patients with autoimmune diseases, as well as in patients receiving immunosuppressive drugs, as this nutraceutical is believed to "activate the immune system." (63) However, the effects of the cyanidin-3-glucoside (the bioactive compound in elderberries) on the immune system is complex with anti-inflammatory, anti-allergic, and immunomodulatory properties. In a human intestinal cell line model, Serra et al demonstrated that cyanidin-3-glucoside (C3G) was effective in inhibiting the release of cytokine-induced proinflammatory mediators. (65) In a murine rheumatoid arthritis model, C3G reduced the concentrations of the inflammatory cytokine IL-6 and IFN-γ and increased the levels of the anti-inflammatory cytokine IL-10 in the peripheral blood and synovial fluid. (66) Pyo et al demonstrated that C3G suppressed IL-4 and IL-13 produced by activated Th2 cells. (67) The preferential switching from a Th2 to a Th1 response may be particularly important in limiting the severity of RSV infection and elderberries may be a valuable treatment modality in patients with allergic diathesis. While the data is somewhat contradictory the preponderance of evidence suggests that elderberries have anti-inflammatory properties; this suggests that this nutraceutical is likely safe in patients with autoimmune disease when used for 2 weeks or less. However, such patients need to monitor their symptoms closely.

Resveratrol or a Combination Flavonoid supplement

- **Dosing and administration**
  400-500 mg daily.

  Generally, the oral bioavailability of resveratrol is poor. (68) However, a bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

- **Mechanisms**
  Resveratrol is a plant phytochemical (flavonoid) that has remarkable biological properties. (69-71) Most importantly it binds to the spike protein and activates autophagy (the body's process of clearing out damaged cells and replacing them with healthy, newer cells). (72, 73) In addition, resveratrol has anti-inflammatory, antiviral, antioxidant, and anticoagulant properties and has beneficial effects on the microbiome.

  Quercetin, a plant flavonoid with many of the biological properties of resveratrol, acts synergistically with resveratrol and remarkably increases the bioavailability of resveratrol. (74-76)

  Pterostilbene is another plant flavonoid similar to resveratrol in structure with similar biological properties. (77-79) However, pterostilbene's unique structure makes it more oil-soluble than resveratrol, which increases its absorption and cellular uptake while reducing the rate of elimination from the body. Research has shown that pterostilbene has seven times the half-life of resveratrol and has greater bioactivity in reducing the effects of oxidative stress. Therefore, we suggest a "high quality" combination supplement with resveratrol and quercetin and ideally also containing pterostilbene.

- **Cautions and contraindications**
  The safety of these phytochemicals has not been determined in pregnancy and they should therefore be avoided. Due to the possible drug interaction between quercetin and ivermectin, these drugs should not be taken simultaneously (i.e., should be staggered morning and night). The use of quercetin has rarely been associated with hypothyroidism. (80) The clinical impact of this association

may be limited to those individuals with pre-existent thyroid disease or those with subclinical thyroidism. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored.

Coffee

- **Dosing and administration**
  One to two cups per day of coffee reduces the risk and severity of infection with SARS-Cov-2 and its variants. (81) Decaffeinated coffee has similar effects to filtered caffeinated coffee with the suppressive activity not being affected by coffee additives. (81)

- **Mechanism**
  Data from the UK Biobank reported that coffee intake was associated with lower risk of infection with COVID-19. (82) Wu et al demonstrated that coffee inhibits multiple variants of the SARS-CoV-2 infection by restraining the binding of the SARS-CoV-2 spike protein to human angiotensin-converting enzyme 2 (ACE2) and reducing transmembrane serine protease 2 (TMPRSS2) and cathepsin L (CTSL) activity. (81) They demonstrated that ground coffee at 6 mg/ml had the effect of reducing the entry of SARS-CoV-2 into host cells with an inhibition of about 60 to 81% in a dose-dependent manner. Similarly, different brands of instant coffee significantly inhibited cell entry of SARS-CoV-2 at 1 mg/ml.

Ivermectin

Ivermectin has strong evidentiary support as a preventative against contracting COVID. (83-87) Data suggests that once a cumulative dose in excess of 200 mg is achieved, the risk of acquiring COVID-19 approaches zero. However, in the current situation of abundant natural immunity along with the recent circulation of less severe and more highly transmissible variants, **chronic weekly or twice weekly ivermectin prophylaxis is no longer applicable to most people.**

The following prophylaxis approaches with ivermectin can be considered and applied based on patient preference, comorbid status, immune status, and in discussion with their provider:

a. Twice weekly (two times per week) ivermectin at 0.2mg/kg; can be considered in those with significant comorbidities and lack of natural immunity or immunosuppressive states or those with long COVID or post-vaccine syndrome who are not already on ivermectin as treatment.
b. Daily ivermectin just prior to and during periods of high possible exposure such as travel, weddings, conferences, etc.
c. Immediate initiation of daily ivermectin at treatment doses (0.4mg/kg) upon first symptoms of a viral syndrome.

Table 1. How to Calculate Ivermectin Dose

Note that ivermectin is available in different strengths (e.g., 3, 6 or 12 mg) and administration forms (tablets, capsules, drops, etc.). Note that tablets can be halved for more accurate dosing, while capsules cannot.

How much do I weigh?		What dose does the protocol say?			
In pounds	In kilos	0.2 mg/kg	0.3 mg/kg	0.4 mg/kg	0.6 mg/kg
70–90	32–41	6-8 mg	10-12 mg	13-16 mg	19-25 mg
91–110	41–50	8-10 mg	12-15 mg	17-20 mg	25-30 mg
111–130	50–59	10-12 mg	15-18 mg	20-24 mg	30-35 mg
131–150	60–68	12-14 mg	18-20 mg	24-27 mg	36-41 mg
151–170	69–77	14-15 mg	21-23 mg	27-31 mg	41-46 mg
171–190	78–86	16-17 mg	23-26 mg	31-35 mg	47-52 mg
191–210	87–95	17-19 mg	26-29 mg	35-38 mg	52-57 mg
211–230	96–105	19-21 mg	29-31 mg	38-42 mg	58-63 mg
231–250	105–114	21-23 mg	32-34 mg	42-45 mg	63-68 mg
251–270	114–123	23-25 mg	34-37 mg	46-49 mg	68-74 mg
271–290	123–132	25-26 mg	37-40 mg	49-53 mg	74-79 mg
291–310	132–141	26-28 mg	40-42 mg	53-56 mg	79-85 mg

Table 2. Guidance on Upfront Loading Dose Regimens to Replenish Vitamin D Stores in the Body

When serum Vitamin D levels are available, the doses provided in this table can be used for the longer-term maintenance of serum 25(OH)D concentration above 50 ng/mL (125 nmol/L). The table provides the initial bolus dose, weekly dose, frequency, and duration of administration of oral Vitamin D in non-emergency situations, in a non-obese, 70 kg adult.

Serum Vitamin D (ng/mL) **	Vitamin D Dose: Using 50,000 IU Capsules: Initial and Weekly $		Duration (Number of Weeks)	Total Amount Needed to Correct Vit. D, Deficiency (IU, in Millions) #
	Initial Bolus Dose (IU)	Follow-Up: $$ The Number of 50,000 IU Caps/Week		
<10	300,000	×3	8 to 10	1.5 to 1.8
11–15	200,000	×2	8 to 10	1.0 to 1.2
16–20	200,000	×2	6 to 8	0.8 to 1.0
21–30	100,000	× 2	4 to 6	0.5 to 0.7
31–40	100,000	×2	2 to 4	0.3 to 0.5
41–50	100,000	×1	2 to 4	0.2 to 0.3

Source: Nutrients'—Special Issue: "Vitamin D—Calcifediol and COVID" (88)

* A suitable daily or weekly maintenance dose to be started after completing the loading-dose schedule. The dose should be adjusted for those who are overweight (higher) or underweight (lower). ** To convert ng/mL to nmol/L, multiply the amount in ng by 2.5; One µg = 40 IU. $ Mentioned replacement doses can be taken as single, cumulative doses, two to three times a week spread out over a few weeks. $$ From day one of week two onwards. # Estimated total Vitamin D dose needed to replenish the body stores (i.e., the deficit) is provided in the last column.

Table 3. Vitamin D Dosing in the Absence of a Baseline Vitamin D Level

Longer-term maintenance schedules of oral Vitamin D based on body weight to maintain the levels above 50 ng/mL (125 nmol/L) when the serum 25(OH)D concentrations are unknown.

Bodyweight Category		Dose kg/Day (IU)	Dose (IU) (Daily or Weekly) *	
(Age) or Using BMI (for age > 18) (kg/Ht. M^2)	Average Body Weight (kg)		Daily Dose (IU)	Once a Week (IU)
(Age 1–5)	5–13	70	350–900	3000–5000
(Age 6–12)	14–40	70	1000–2800	7000–28,000
(Age 13–18)	40–50	70	2800–3500	20,000–25,000
BMI ≤ 19	50–60 (under-weight adult)	60 to 80	3500–5000	25,000–35,000
BMI < 29	70–90 (normal: non-obese)	70 to 90	5000–8000	35,000–50,000
BMI 30–39	90–120 (obese persons) #	90 to 130	8000–15,000	50,000–100,000
BMI ≥ 40 $	130–170 (morbidly obese) $	140 to 180	18,000–30,000	125,000–200,000

Source: Nutrients'—Special Issue: "Vitamin D—Calcifediol and COVID" (88)

* Example of a daily or once-a-week dose range for adults with specific body types (based on BMI for white Caucasians and body weight for other ethnic groups). Appropriate dose reductions are necessary for children. # For those with chronic comorbid conditions, such as hypertension, diabetes, asthma, COPD, CKD, depression, and osteoporosis, and to reduce all-cause mortality, higher doses of Vitamin D are needed. For them, one can use the doses that are recommended for persons with obesity (BMI, 30–39: the third row). $ Those with multiple sclerosis, cancer, migraine headaches, and psoriasis, and those routinely taking medications such as anti-epileptic and anti-retroviral agents that significantly increase the catabolism of Vitamin D should consider taking age-appropriate doses recommended for those with morbid obesity (BMI ≥ 40; the higher end of the daily doses in the fourth row).

Post-Exposure Prevention

How to prevent infection if you have potentially been exposed

Naso-Oropharyngeal hygiene (Nasal Spray and Mouthwash)

The combination of nasal antiseptic sprays and oropharyngeal mouthwashes is strongly suggested. Influenza, SARS-CoV-2, RSV, and almost all other respiratory viruses replicate primarily in the nasopharynx. A 1% povidone-iodine nasal spray or a spray with Iota-Carrageenan are potent inhibitors of SARS-CoV-2 and influenza virus, and dramatically alter the course of infections with these viruses. (89-95)

- **Dosing and administration**
  Spray nose and gargle with mouthwash, 2-3 times daily.

  A nasal spray with 1% povidone-iodine (for example Immune Mist™, CofixRX™ or Ionovo™) administered 2-3 times per day is recommended in post-exposure prophylaxis. [8] Nasal irrigations with saline, as well as neutral electrolyzed water, have been shown to be beneficial, (96, 97) as well as a Nitric Oxide (NO) nasal spray. (98)

  We suggest using a mouthwash/gargle in addition to a nasal spray. We recommend products containing chlorhexidine, povidone-iodine, or cetylpyridinium chloride or the combination of eucalyptus, menthol, and thymol. Gargle with these solutions 2-3 times/day.

- **Mechanisms**
  In patients with symptomatic COVID-19 treating at home with a 1% povidone-iodine mouthwash/gargle, together with nasal drops, resulted in a dramatic reduction in morbidity, hospitalization, and death. (89) Antiseptic-antimicrobial mouthwashes have been demonstrated to inhibit replication of multiple respiratory viruses, including SARS-COV-2, influenza, respiratory syncytial virus, etc.
- **Cautions and contraindications**
  Due to low-level systemic absorption, pregnant women should not use povidone-iodine nasal sprays for longer than 5-7 days. While the use of an iodine-containing mouthwash over a six-month period was demonstrated to increase serum iodine levels, thyroid function tests remained unchanged. (99) It should however be noted that the Ionovo™ spray contains iodine in an amount equivalent to the daily dietary requirement and hence Ionovo Iodine is safe to ingest. In addition, Ionovo Oral Iodine is a "100% natural molecular iodine". If tooth staining occurs, discontinue use of mouthwash and try another product.

Elderberry

- **Dosing and administration**
  Four times daily as per manufacturer directions for 1 week (gummy, supplement, or syrup).

Vitamin C

- **Dosing and administration**
  500-1000 mg four times daily for 1 week.

Elemental Zinc

- **Dosing and administration**
  50-90 mg daily for 1 week.

Melatonin

- **Dosing and administration**
  2-5 mg at night (slow/extended release)

Resveratrol/Combination Flavonoid supplement

- **Dosing and administration**
  500 mg twice daily.

Optional with documented exposure to COVID-19 (positive test)

a. Ivermectin: 0.4 mg/kg immediately, then repeat second dose in 24 hours.
b. Hydroxychloroquine (HCQ): 200 mg twice a day for 5 days. OR
c. Nitazoxanide 500-600 mg twice daily for 5 days.

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