Decontaminating the Nose, Mouth and Throat of SARS-CoV-2 with Povidone-Iodine – Aren't We Missing Out on Very Effective Prevention and Prophylactic Tools in the War Against the Covid-19 Pandemic?[Ω]

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Abstract

Background: An outbreak of a new coronavirus, the SARS-CoV-2 (or Covid-19) has resulted in more than two million infected people and tens of thousands of deaths (the situation quickly evolves on daily basis). Fortunately, majority of patients experience only mild upper respiratory tract symptoms, or no symptoms at all, loss of smell and taste being the predominant complaint.

But, unfortunately, even asymptomatic individuals can unknowingly spread the infection, which makes the pandemic very difficult to get under control. While lockdowns for entire country populations have shut down economies and international trade, the WHO has warned they may not be enough despite their high long-term economic and social costs.

However, *little* or *no* scientific information has circulated reviewing already existing effective science- and evidence-based preventive/prophylactic measures that "kill" SARS-CoV-1 and are likely also to inactivate the current SARS- CoV-2.

Our personal communication aims to fill this void.

Method: First, we review the scientific literature and the evidence on preventive/prophylactic measures that neutralize SARS-CoV-1 virus. Second, our analysis looks into the scientific evidence on the use of povidone-iodine (PVP-I) in mouthwash/gargling/spray forms, as these represent the only innovatively developed, tested and available *practical* solution to inactivate SARS-CoV viruses (e.g. SARS-CoV-1, Middle-East Respiratory Syndrome virus or MERS, and SARS-CoV-2).

Findings: Multiple evidence (mainly in vitro/cell cultures) demonstrate that the use of *povidone-iodine* (PVP-I) inactivates SARS-CoV-1 in matter of seconds. Preliminary test results suggest it may also similarly "kill" the current new SARS-CoV-2.

Discussion: The use of PVP-I for decontamination of the nose/mouth/throat has a well-established tolerability profile, is low-cost and has limited downside risks. It is an evidence-based and highly cost-effective health intervention. Our analysis suggests that PVP-I utilization merits being considered as an additional preventive measure (in clinical and in population settings) against getting infected by, and infecting others with, the current SARS-CoV-2 virus.

[Ω] This article is a *personal* communication engaging nobody else than the authors. Our intention is to inform the scientific debate. Any remaining errors remain ours. *Contact:* dlubomirov@protonmail.com.

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Background

An outbreak of a new coronavirus, the SARS-CoV-2 (or Covid-19), first in Wuhan (China) then spreading worldwide, has resulted in more than two million infected people and tens of thousands of deaths (the situation quickly evolves daily basis). It mainly affects the respiratory system and in serious cases leads to acute pneumonia, respiratory distress and severe drop of blood oxygen level, which are critical and require hospitalisation and intensive care treatments.

Although the respiratory distress (dry cough, shortness of breath, fatigue, fever) symptoms are the principal clinical features in hospitalised patients, evidence is accumulating that Covid-19 infection begins in the upper respiratory tract. In majority of cases, the initial symptoms that patients report are loss of smell and taste [25], which the British Rhinology Society [10] suggests should be used as a screening tool for early infection detection. In patients with mild disease, anosmia is the main complaint and the timing of its resolution matches the recovery from the Covid-19 infection [17].

The principle response by Governments and Health authorities in Europe and most of the world is to introduce and enforce Quarantine measures for *entire* country populations, in order to limit the spread of the pandemic. This approach, if extended for any lengthy period, creates additional health, social and economic burden by shutting down national economies and international trade; and putting societies at enormous risks of financial and monetary breakdowns and economic hardship. Moreover, as reported by Reuters [21], according to a WHO expert [24], lockdowns may not be "enough to defeat the virus" despite their high social costs.

But *little* or *no* scientific information [16] has circulated about already existing effective science- and evidence-based preventive/prophylactic measures and interventions, that are likely to "kill" the new virus.

Method

This short analysis aims to *fill* this void by looking into the efficacy/effectiveness of preventive measures for SARS-CoV-1 that could also be expected to inactivate SARS-CoV-2. It is limited to research into *prevention/prophylactic* interventions, rather than research of *curative* treatments of Covid-related pneumonia and severe respiratory syndrome that may cause infected peoples' death.

- **First**, the analysis includes an overview of the publicly available studies of neutralizing SARS-CoV-1 virus, which can be useful for inactivating the *current* SARS-CoV-2 virus.

  Most of the (*in vitro/cell cultures*) measures found to kill SARS-CoV-1 are simple on paper. Despite that simplicity, few *practical* applications have been developed for prophylactic use by the medical profession on the front-line, or by the general public. At present, only but one of the existing preventive measures "killing" SARS-CoV-1, have been tested in the specific context of the *current* SARS-CoV-2, there is high probability that they all may remain effective in inactivating also the new strain.

- **Second**, this analysis specifically focuses on one of those preventive measures - the innovative prophylactic use of *povidone-iodine* (PVP-I), a substance widely used as antiseptic since the mid-1950s and known for its safe and very broad-spectrum activity against all types of pathogens, notably all types of viruses. Our review of the scientific research shows that PVP-I products, due to continuous innovation over the last decades, are particularly effective in inactivating SARS-CoV-1 (and also Middle-East Respiratory Syndrome-CoV or MERS) while being particularly safe for use by humans in different forms, *including for viral decontamination of the nose, mouth and throat with mouthwash/gargle/spray application, especially relevant in the case of the current SARS-CoV-2 virus*.

Given that no vaccine or other treatment is in view and that PVP-I may be also highly effective in neutralizing the *current* SARS-CoV-2 (with a low cost and risk), not only scientific-evidence, but also common sense, dictate to consider its prophylactic use in the current situation to prevent people from getting infected, and from infecting others, minimising the spread of the pandemic.

Findings

What "kills" SARS-CoV-1: an overview

The SARS-CoV-1 outbreak of 2002-03 resulted in 8000 cases and 800 deaths (see Table 1).

Table 1: SARS-CoV-1 infected cases and deaths [1]

Country	Total	Median Age	Deaths	Case fatality Ratio (%)	First Case	Last Case
China	5327	na	349	7 %	Nov-02	Jun-03
Hong Kong	1755	40	299	17 %	Feb-03	May-03
Taiwan	346	42	37	11 %	Feb-03	Jun-03
Singapore	238	35	33	14 %	Feb-03	May-03
Vietnam	63	43	5	8 %	Feb-03	Apr-03
Indonesia	2	56	0	0 %	Apr-03	Apr-03
Malaysia	5	30	2	40 %	Mar-03	Apr-03
Thailand	9	42	2	22 %	Mar-03	May-03
Philippines	14	41	2	14 %	Feb-03	May-03
Total	**8096**		**774**	**9,6 %**		

Table 2 below summarizes the main scientific evidence about the different measures and methods that were found to "kill" SARS-CoV-1, rendering it non-infectious. But new research is *highly needed* to test and rapidly diffuse similar scientific information and knowledge about the methods inactivating the current SARS-CoV-2 (e.g. at what temperature SARS-CoV-2 is inactivated [19]).

However, few if any *practical* applications for potential prophylactic use by humans in *real world* conditions have been developed based on the above knowledge to diminish the viral load in the nose/mouth/throat and prevent infection or minimise the disease caused by SARS-CoV coronaviruses. One exception is the development, testing and availability of PVP-I use for *oropharyngeal* or *nasal* protection against such viral infections which are particularly relevant for protection in the case of the current SARS-CoV-2.

Table 2: Prophylactic methods inactivating SARS-CoV-1 (in vitro/cell cultures)

Reference	Methods & conditions killing SARS-CoV-1
WHO (2003) [24]	*Heat at 56°C* kills the SARS-CoV coronavirus at around 10,000 units *per 15 min* (i.e. a quick reduction)
Kariwa et al. (2006) [14]	•*PVP-I products* reduce the virus infectivity to below detectable level in *2 min* •*70% ethanol*: its efficacy is similar to that of PVP-I •*Fixatives including formalin, glutaraldehyde, methanol and acetone* for *5 min* eliminate all infectivity •*Heat at 56°C* for *60 min* reduces the infectivity of the virus to undetectable levels •*Irradiation with ultraviolet light at 134 microW/cm2* for *15 min* reduces greatly the infectivity; however, prolonged irradiation (*60 min*) fails to eliminate the remaining virus, leaving 18.8 TCID50/ml
Duan et al. (2004) [4]	•*Heat* renders the virus non-infectious on different surfaces at: *56°C* for *90 min*; *67°C* for *60 min*; *75°C* for *30 min* •*Irradiation* of UV results in destruction of viral infectivity to undetectable levels
Chan et al. (2011) [1]	•*Heat* at 38°C in relative humidity of >95% diminishes virus viability (on smooth surfaces)
Darnell et al. (2004) [3]	The virus is inactivated by: •Ultraviolet light (UV) at *254 nm* •Heat treatment of *65 °C* or greater •Alkaline (*pH >12*) or acidic (*pH < 3*) conditions •Formalin and glutaraldehyde treatments

PVP-I broad-spectrum anti-viral potential

PVP-I presents a unique combination of:

- *Very broad-spectrum antiseptic power*: it has been found to be effective against bacteria, fungi and many viruses, including SARS-CoV-1, killing it in only *2 minutes, or less* [14]
- *Safety in use and high tolerability:* PVP-I has been in use for almost 60 years and its safety profile is well-established. PVP-I products have few counter-indications (e.g. on thyroid function after prolonged long-term use, or a low risk of allergy to iodine) and are safe for prophylactic use under proper instructions, both externally, e.g. on the skin, and, due to *innovation*, internally for nasal [8] and oropharyngeal use (mouthwash/gargle/spray form) [13].

Table 3 below summarizes the main the evidence of the anti-viral potential of PVP-I products, tested in such forms and concentrations that are *already* available in many countries and are used on a daily basis.

Table 3: Evidence of PVP-I *anti-viral* potency (e.g. in respiratory infections)

Reference	Virus	Method and PVP-I product	Evidence of PVP-I anti-viral potential
Kariwa et al. (2006) [14]	SARS-CoV-1	In vitro antiviral activity of: PVP-I 1% solution PVP-I 1% Scrub PVP-I 0.25% Palm PVP-I 0.47% Gargle PVP-I 0.23% throat spray	Virus infectivity is reduced to below detectable level in *2 min*
Ito et al. (2006) [11]	Avian influenza A virus (H5N1)	In vitro antiviral activity of: 2% PVP-I solution 0.5% PVP-I scrub 0.25% PVP-I palm 0.23% PVP-I gargle 0.23% PVP-I throat spray 2% PVP-I solution (for animals)	• Viral infectivity is reduced to below detectable levels after *10 seconds* • Results "indicate that PVP-I products have virucidal activity against avian influenza A viruses. Therefore, the PVP-I products are useful in the prevention and control of human infection by avian influenza A viruses."
Eggers et al. (2018) [6]	SARS-CoV-1 MERS-CoV Influenza virus A (H1N1) Rotavirus (Wa strain)	In vitro antiviral activity of: PVP-I 7% gargle/mouthwash diluted with water to a concentration of 0.23% (the recommended concentration for "real-life" use in Japan)	• Rapid virucidal efficacy inactivating SARS-CoV, MERS-Covid, influenza virus A (H1N1) and rotavirus after *15 seconds of exposure* • PVP-I "may provide a protective oropharyngeal hygiene measure for individuals at high risk of exposure to oral and respiratory pathogens."

The authors of a 2015 overview [13] regarding the practical prophylactic use of PVP-I products in the prevention and treatment of infections, highlight:

> "PVP-I products, that included *gargle and throat spray*, demonstrated *rapid virucidal activity* against both a highly pathogenic (H5N1) and low pathogenic (H5N3, H7N7 and H9N2) strains of avian influenza A viruses, with viral titres falling below the detection limits of the assay with only *10 s* of PVP-I incubation. Similarly, these formulations also *showed efficacy* against a *severe acute respiratory syndrome coronavirus* strain, with PVP-I mediating rapid inactivation of the virus (*2 min of treatment*). Furthermore, the results of a study confirmed the virucidal efficacy of PVP-I products including PVP-I gargle against swine influenza viruses (H1N1, H3N2 and H1N2). (...)
>
> Gargling, intensified by the presence of PVP-I, may therefore play an *important role* in the prevention or reduction in the incidence of infection through droplet transmission.
>
> Indeed, the benefit of gargling with PVP-I has been noted in Japanese clinical respiratory guidelines that recommend gargling with PVP-I (four times a day) in both inpatients and healthcare workers for the prevention of hospital-acquired pneumonia. PVP-I has also been recommended as a preventive measure against pandemic influenza. (...)

> These studies provide a *strong rationale* for the use of PVP-I as an *effective oral care* measure to reduce the burden of potential pathogens and minimise the risk of infection in *both* community-acquired and hospital-acquired settings." (ital. added)

An Australian outlet has reported that new evidence shows that PVP-I — in the form of a safe nasal spray, currently in the *final* Phase III of the regulatory approval process — also inactivates the *current* SARS-CoV-2 virus [20]:

> "Melbourne-based biotech company (...) has developed a "disinfectant for your nose" that could be capable of reducing the amount of detectable coronavirus by *almost 100 per cent*.
>
> In a report seen by The Australian Financial Review, laboratory tests in a test tube showed its nasal spray, *reduced the amount of detectable coronavirus by 99.97 per cent and eliminated the infectious properties of any remaining virus*." (ital. added)

The product is waiting for approval by Australian regulatory authorities [as of date of writing]. Such a product is an opportunity for fast and immediate testing in all countries that suffer from the pandemic. Given the long-standing record of PVP-I efficacy in "killing" SARS-CoV-1 and MERS coronaviruses (as well as other pathogens) and its safety record, PVP-I nasopharyngeal hygiene products can be useful as preventative and prophylactic interventions, limiting the spread of the pandemic, until a vaccine or other permanent effective and safe solution is developed.

The scientific evidence about the effectiveness of PVP-I suggests that, in real world conditions, it may inactivate SARS-CoV-1, MERS, and even the current SARS-CoV-2, in matter of seconds and, thus, reduce the *viral load* in the nose, mouth, or throat. However, more testing is needed to confirm the degree of effectiveness and to establish the best protocols for real life use by patients, healthcare professionals and the general public, since there are different cultural habits regarding gargling and the use of PVP-I for oropharyngeal decontamination.

For example, in the context of their national campaign to control epidemics, (e.g. the pandemic of influenza) the Japanese Ministry of Health, Labour and Welfare used to recommend, at least as recently as 2007, for professionals and the general population to wash their hands and to *gargle* along with other standard hygiene measures such as using face masks, and social distancing [12].

Discussion

There are multiple preventive measures/methods that, based on the scientific literature "kill" SARS-CoV-1, e.g. the use of UVC [23]. But new research is *urgently* needed to update our knowledge and validate which methods remain effective, and to what extent, against the current strain SARS-CoV-2.

The use of PVP-I is among those methods and it is well-known for its effectiveness in decontaminating and 'killing' pathogens on the external parts of the body and the skin. But, more relevant in the context of the current "war", it is also found to inactivate SARS-CoV-1, MERS; preliminary results show it may similarly "kill" in *seconds* the current SARS-CoV-2.

However, the real-world evidence (*in vivo*) of their effectiveness in the form of mouthwashes/gargles/sprays for the decontamination of the nose, mouth and throat, is rather scarce. An epidemiological study about the transmissibility among infected persons could provide such evidence, which would be particularly useful in understanding the progression of the infection depending on the viral load. The study could include asymptomatic cases with or without anosmia (whose tests are positive), mild-symptomatic cases and hospitalised cases who are assumed to be the most contagious group due to their maximally high viral load. The evidence collected in relation to the Australian nasal spray may provide decisive evidence in that regard.

Also, while the virus may take only few minutes to penetrate inside a cell, new research is needed to establish whether PVP-I is effective once the virus is inside the cell, whether PVP-I should already be present on the mucous membranes before infection occurs, or what precisely happens once the virus is released by the infected cell. In the latter case, new research should inquire how long PVP-I remains protective after spraying, mouth-washing or gargling against *outside* viral attack, or against virus particle release from *already* infected cells. If still present on the mucous surfaces at this key-stage of viral multiplication, PVP-I could potentially reduce the viral load, limit the progression of the disease and minimise the spreading of the infection.

The use of PVP-I is aimed to be preventive and possibly be used as initial stage prohylactic intervention, applied at first appearance of the upper respiratory tract symptoms. It is difficult to envisage an effective nasal spraying or gargling for persons undergoing emergency intensive care treatments (i.e. once the virus has already spread to the lungs).

In any case, given the little or downside risks when properly used (after verifying for the absence of allergy to iodine, or for thyroid conditions), *frequent PVP-I rinsing, gargling, spraying (or applying a palm in the nose)* could be recommended in most cases, for example, a family with an already confirmed Covid-19 case. While in hospital settings healthcare workers are usually well-protected, the use of PVP-I could represent an additional preventive tool, as is the case in Japan and other Asian countries.

The author of a mid-2019 article [7] on *Infectious Disease Management and Control with PVP-I* conclude their analysis in the following terms:

> "Studies have shown that hand washing with PVP-I-based antiseptics is effective for the decontamination of skin, while *PVP-I mouthwashes and gargles significantly reduce viral load in the oral cavity and the oropharynx*. The importance of PVP-I has been emphasised by its inclusion in the World Health Organization's list of *essential* medicines, and *high potency for virucidal activity* has been observed against viruses of significant *global* concern, including hepatitis A and influenza, as well as the *Middle-East Respiratory Syndrome* and *Sudden Acute Respiratory Syndrome coronaviruses*. Together with its diverse applications in antimicrobial control, broad accessibility across the globe, and outstanding safety and tolerability profile, PVP-I offers an *affordable, potent, and widely available antiseptic option*. "(ital. added).

Given the minimal additional risk and its low cost, the use of PVP-I appears worth considering [16], among healthcare workers, in the military, and at population-level.

The current context of *uncertainty* requires a quick but rational decision, based on what we already know about PVP-I and given the absence of other effective preventive tools for the nose/mouth/throat. An application, *mutatis mutandis*, of Type I/Type II error analysis [18] suggests that the costs of waiting for a definitive proof of PVP-I effectiveness, and not acting based on the current evidence, are extremely high (see Type II error in Table 4 below). On the contrary, the downside risks and costs of considering PVP-I use, based on the current knowledge, are very low (Type I error).

Table 4: Decision Analysis under uncertainty of the effectiveness and potential harm of PVP-I use for SARS-CoV-2 infection & pandemic

	UNCERTAIN FUTURE STATES OF THE WORLD	
	PVP-I PROVED NOT EFFECTIVE	**PVP-I IS EFFECTIVE**
NO CONSIDERATION	**RIGHT DECISION** (PVP-I NOT used) **Costs:** *none* **Benefits:** *~none* (i.e. *avoided* low financial costs and low health risks)	**TYPE II ERROR** (PVP-I NOT used) **Costs:** • **Health:** high morbidity & mortality • **Socio-economic:** unprecedented financial, economic and social costs due to unnecessary prolonged lockdowns
CONSIDERATION	**TYPE I ERROR** (PVP-I IS used) **Costs:** • **Health:** *low* risks (e.g. alergy, thyroïde complications) • **Socio-economic:** *low additional expenditure*	**RIGHT DECISION** (PVP-I IS used) **Costs:** *low* health risk & *low* economic cost **Benefits:** • **Health:** *avoided* high morbidity & mortality • **Socio-economic:** *avoided* financial, economic and social severe costs; shorter delays to returning to normal life

The use of PVP-I as preventative and prophylactic measure should be high on the list of preferred options (in addition to the recommended hand washing or mask wearing) for all uninfected, infected-asymptomatic, as well as people with minimal initial upper respiratory tract symptoms. This could contribute to reducing the viral load [8] in exposed individuals and preventing the further development of the later critical stage of infection and disease.

But the use of PVP-I could also reduce the viral transmission to others, slowing and limiting the outbreak of SARS-Covid-2 throughout the population of a community, town, region, country and the whole world.

As stressed by Eggers et al. [4]:

> "Given the strong in vitro virucidal activity (…) PVP-I may be an effective measure to disrupt the transmission of respiratory viruses, especially via airborne/droplet transmission or after uptake via the mouth (such as when touching the mouth or food with contaminated hands).

The preventive/prophylactic use of PVP-I products holds a great potential for protecting vulnerable populations, and especially the health workers on the front-line of the current pandemic, who are constantly exposed to high viral loads. PVP-I nose, mouth and throat hygiene applications could be part of their approved Personal Protective Equipment, reducing infection and deaths of health workers, reducing the pressure on the health systems and contributing to bring the pandemic under control. This is especially pertinent as most countries plan to remove progressively the lockdowns, increasing the risk of a second wave of infections with the current lack of proper prevention tools.

More research is needed to find the best dosage, forms and method of administration, as well as practical protocols for different healthcare settings (for the context of the UK, see [15]) and the general population in different contexts such as business offices, hotels, bars, restaurants, shops, sports clubs and wellness or conference centres.

Declaration of interest: none.

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