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Povidone iodine as a low cost therapeutic against the SARS-CoV-2 virus and its potential for refugee health

Abstract

This review summarizes one approach to support the health needs of refugee and displaced asylum seeker migrant populations during the SARS-CoV-2 pandemic. Refugees are the leading abandoned group during pandemic crises and their health needs are always at greater risk. Living conditions are unsettled and there is often limited access to health facilities and to necessary infection control measures to control viral spread. Therefore, access to and provision of economical, safe, and effective antiseptic options must be addressed for better community health and for the reduction of viral transmission. Recent research on povidone-iodine, PVP-I supports its use as a potent, topical virucidal antiseptic against SARS-CoV-2 at the 99% level. This paper summarizes the evidence from both *in vitro* and *in vivo* research. Generalizing across the studies shows that PVP-1 used as a mouth wash, oral rinse, or a gargle can reduce viral load. Because of its cost-effectiveness and high virucidal activity, PVP-I can be used as an effective self-care antiseptic in the refugee population.

Keywords: povidone iodine, refugee, therapeutic, SARS-CoV-2, COVID-19, antiseptics

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Introduction

Around two years into the pandemic, official figures from the United Nations High Commissioner for Refugees (UNHCR) reported nearly 82.4 million people worldwide were forcibly displaced because of human rights abuse, violence, conflict, disaster displacement, or public order disturbances.[1] Currently, however, there is no exact figure on the number of refugees who have contracted COVID-19?

For many such as the Rohingya refugees in Bangladesh, nearly one million people live in camps in Cox's Bazar.[2] In the world's largest and most densely populated camp, sanitation conditions are poor, and overcrowded tent city accommodation is the norm. With up to 45,000 people per square kilometer, there is limited access to clean water and infection control is challenging, despite a limited vaccine rollout that began in August 2021. For refugees and frontline health workers, putting public health into practice is difficult. Here, social distancing, stay-at-home orders, and mask mandates are nearly impossible to practice; and may be of limited effectiveness even if they were possible to apply. Often refugees have underlying health conditions and nutritional deficiencies. Coupled with poor health infrastructure, stress, mental health pressures and uncertainty and hesitancy around vaccination, there is potential for devastation especially if there is an outbreak of COVID-19 variants.[3]

Studies on migrants and forcibly relocating groups have reported a negative impression towards lockdown strategies with consequences for mental health.[4] Recent research on displaced persons in refugee camps has confirmed that lockdowns and social distancing recommendations are difficult to implement. The conclusions were that xenophobia and discrimination are common, and many refugees are targeted as carriers of the virus, with many stigmatized as spreaders of disease.[5] Social controls like physical distancing and mass quarantine in refugee accommodation won't necessarily lead to a decrease in SARS-CoV-2 infections. Paradoxically, an increase in COVID case numbers was seen in mass quarantine.[6]

Another study focused on the awareness of COVID-19 in older people (>60 years) in the Rohingya community. Results showed there is little fear of contracting the virus but that is probably because of a lack of understanding about the severity of the disease. The authors concluded it is important to distribute actual public health information to improve knowledge among older persons and to prevent further deterioration of health because of COVID-19 infection waves.[7] A similar survey in Somali camps revealed that nearly one in two people did not have basic information about the virus or were not confident they could receive medical care if infected.[8] Another recent commentary summarized that refugees and asylum seekers face many vulnerabilities around COVID-19, including fear of contacting the healthcare system, difficulties with cultural imbalances, food insecurity, discrimination, health illiteracy, and a lack of readily available, or culturally appropriate educational materials.[9] There is also increasing migratory pressure in hotspots like Afghanistan[10] and for the ten million people who have already fled their homes in Ukraine where instability could prompt an unplanned exodus. Although introducing vaccination programs appears relieving, it may be many months until herd immunity is reached.[11] The African population is also one of the leading neglected groups where only less than 1% of the population is vaccinated due to deficient global solidarity around development assistance.[12]

The purpose of this paper is therefore to review the use of povidone-iodine, PVP-I as an economical, accessible, effective, and self-delivered therapeutic as an infection control strategy against the SARS-CoV-2 virus.

SARS-CoV-2 and the case for an economical antiseptic based on iodine

The sudden outbreak of COVID-19 towards the end of 2019 is the leading global health emergency of our time. Despite early effectiveness of novel vaccines against SARS-CoV-2, the emergence of new variants along with unanticipated side effects, means there is a need to identify and evaluate alternative, complementary approaches. One method is to look at therapeutics like antiseptics and disinfectants that are inexpensive and easily sourced.[13–15] SARS-CoV-2 is spread through droplets, bioaerosols and fomites which enter the respiratory

system through the oral or nasal cavity.[14] This paper therefore focusses on the topical antiseptic Povidone-iodine (PVP-I) which has known virucidal activity against respiratory viruses. For example, PVP-I has an excellent viricidal response against many respiratory viruses including Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and influenza[13,16] Current evidence also supports its virucidal response against severe acute respiratory syndrome coronavirus (SARS-CoV).[13] Recent research demonstrates effectiveness against SARS-CoV-2 both *in vitro* and *in vivo*.[13] This mini review will summarize the literature and demonstrate support for the use of PVP-I as a safe topical nasopharyngeal antiseptic. It is hoped this information will improve refugee health status during the COVID pandemic and more generally against other respiratory virus pathogens.

Recent research evidence

A literature survey on Medline/PubMed was used to identify studies where povidone-iodine (PVP-I) has been evaluated for its virucidal activity against SARS. Table 1 demonstrates selected *in vitro* and *in vivo* studies using PVP-I (Table 1).

Table 1 Overview of selected studies

S. no.	Author, year, & reference No.	PVP concentration	Testing methodology	Patient group	Outcome
1	Liang B, et al.[17]	Povidone iodine (PVP-I): 1.0 % and 0.6% (gel forming nasal spray ophthalmic eye drop)	*in vitro* (VERO76 cells)	SARS-CoV-2 (strain USA_WA1/2020)	Different dilutions were incubated at 37°C. Log reduction was concluded at all time frames at 30sec, 2min and 10min. Both agents were potent to reduce viral load of eye and nasal passage
2	Seneviratne C, et al.[18]	PVP-I: 0.5% (Gargle and Mouthwash 10 mg)	*In vivo* RCT	Covid 19 patients: 36	Significant decrease of salivary viral load which was maintained up to 6hr.
3	Xu C, et al.[19]	PVP-I: 1% (10% solution)	*In vitro* (HeLa-hACE2 and epithelial cell lines - oral)	SARS-CoV-2 virus (USA_WA1/2020 strain)	Complete blockage of viral infectivity
4	Anderson DE, et al.[20]	PVP-I: 10% (antiseptic solution), PVP-I: 7.5%(skin cleanser), PVP-I: 1%(gargle and mouth wash) PVP-I: 0.45%(throat spray)	*In vitro* Vero-E6 cells (American Type Culture Collection)	SARS-CoV-2 (hCoV-19/ Singapore/2/2020)	99.99% viricidal response with ≥ 4 log_{10} viral decline after 30sec of contact time
5	Ruiz C, et al.[13]	PVP-I: 1%	*in vitro*	(Narrative review)	significant drop of viral load was reported at 3hr. by rinsing 15 ml solution of PVP-I 1% for 1minute contact time
6	Chopra A, et al.[21]	PVP-I: 0.5%	*In vitro*/ in vivo (gargle/mouth rinse)	Review	30 sec gargles can minimize the load of SARS-CoV-2 virus
7	Köntös Z[22]	Iodine Drops (200 µg iodine/ml)	*in vitro* Vero 76 cells (ATCC CRL-1587)	SARS-CoV-2 (USAWA1/2020 strain)	99% reduction of viral titre
8	Bidra AS, et al.[23]	PVP-I: 0.5%, 0.75%, 1.5% (Oral rinse)	*In vitro* (Vero 76 cells)	SARS-CoV-2, USA-WA1/2020 strain	Viricidal activity achieved at all concentrations within 15sec time
9	Davies K, et al.[24]	PVP-I: 0.58% (mouth washes)	*in vitro* (mouth wash titration)	tissue culture fluid.[TCF] Minimum Essential Media.[MEM] and 5% foetal calf serum	Log reduction of ≥4.1to ≥5.5 log_{10} in viral titre at 1min treatment
10	Arefin MK, et al.[25]	PVP-I nasal spray (NS) at diluted concentrations of.5% and.6%.	*In vivo* (Nasal spray)	Covid 19 patients: 189	Promising outcome by nasopharyngeal clearance with all PVP-I NI and PVP-I NS formulations
11	Blasi C, et al.[26]	PVP-I: 1%	*In vivo* (Gargles, and nasal dropping)	Covid 19 patient: 01	Rapid regression of COVID-19 after nasal instillations and gargles symptoms improvement
12	Pelletier JS, et al.[27]	PVP-I 0.5%, 0.75%, 1.5% oral rinse antiseptic solutions PVP-I 0.5%, 1.25%, 2.5% nasal antiseptic solutions	*in vitro* (nasal and oral) Vero 76 cells	SARS-CoV-2, USA-WA1/2020 strain	99.99% viricidal response was against all concentrations at 60sec of contact time

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Table Continued...

S. no.	Author, year, & reference No.	PVP concentration	Testing methodology	Patient group	Outcome
13	Jain A, et al.[28]	PVP-I: 1% effective concentration	*In vitro* (mouth rinse) cultivation by VeroE6 cell line	SARS-CoV-2 strain	Percent SARS-CoV-2 inactivation, 30sec: 99.8 Percent SARS-CoV-2 inactivation, 60sec: >99.9
14	Hassandarvish P, et al.[29]	PVP-I: 0.5% (gargle and mouthwash) PVP-I 1% (gargle and mouthwash)	*In vitro* Vero E6 cells (American Type Culture Collection)	SARS-CoV-2 (SARS-COV-2/MY/UM/6- 3; TIDREC)	Viricidal activity was evaluated at both dirty and clean settings >4 log10 inhibition at 15sec, and >5 log10 viral inhibition at 30 and 60sec
15	Martı´nez Lamas L, et al.[30]	PVP-I: 1%	*In vivo* (mouth wash)	Covid 19 patients: 04	Significant viral load reduction, effective for 3hr. at least
16	Shet M, et al.[31]	PVP-I: 0.5% (w/v)	*In vitro* (Vero 76 host cells)	SARS-CoV-2, strain USA-WA1/2020	Rapid inactivation of SARS-CoV-2 with contact duration of 15sec.
17	Seikai T, et al.[32]	PVP-I gargle solution: 20 ml	*In vivo* (Gargles)	SARS-CoV-2 Analyzed patients: 11	Significant decreased of viral titers after 60min of gargling
18	Ferrer M. D, et al.[33]	PVP-I: 2%	*In vivo* (Mouthwash)	SARS-CoV-2 patients: 18	No effect on viral salivary load
19	Mendoza J, et al.[34]	PVP-I	Clinical and *in vitro* studies	Mouth washes	Effectiveness seen
20	Garcia-Sanchez A, et al.[35]	PVP-I	*In vivo* studies	Pre-intervention mouthwash	Effective, decrease risk of cross-infection and recommended before procedures in healthcare settings
21	Ashraf S, et al.[36]	Ionic-iodine polymer complex (200 mg of elemental iodine)	interventional arm A: encapsulated, Arm B: suspension syrup form, Arm C: throat spray, Arm X: Placebo	Allocation ratio: 1:1:1:1	Study protocol for RCT

NI, nasal irrigation; NS, nasal spray; RCT, randomized control trial

PVP-I is a high potency antiseptic agent because it inhibits viral receptors like hemagglutinin and neuraminidases N1, N2, and N3. Disrupting host cell attachment by inactivating receptors to limit viral infection is an obvious choice for infection control in community and healthcare settings for both unexposed and higher risk staff.[35] Lungs are the prime receptor organs of ACE2 followed by the oral cavity. The oral cavity is the best potential site of SARS-CoV-2 invasion because of saliva. Human Angiotensin-Converting Enzyme 2 (ACE2) receptors are the binding sites for SARS-CoV-2.[13] Testing mouthwashes containing different concentrations of PVP was the evaluation method of choice among the selected studies.[6,23] In turn, most studies used comparative evaluation and found PVP to be the most effective antiseptic.[33,34]

The guidelines of the Japanese Respiratory Society in 2004 recommended PVP-I mouthwash for admitting patients and health care staff to minimize the risk of hospital-acquired infections and to reduce the proliferation of microbial growth in the oral cavity.[37,38] Many clinical trials also support the practice of PVP-I antiseptic gargles for immune-compromised patients to reduce the risk of oral infections and viral spread.[16] The effectiveness of PVP-I has been repeatedly established against various respiratory viruses such as MERS, influenza, and Ebola viruses.[16] More recent studies have used oral and nasal agents, containing different concentrations of PVP-I to test its efficacy against SARS-CoV-2. The research trials initiated after the Covid-19 outbreak began have mostly reported on *in vitro* efficacy of PVP-I across different concentrations. Other *in vivo* studies have also been conducted on Covid-19 positive patients and high-risk groups to evaluate PVP-1 efficacy against SARS-CoV-2.

In vivo Efficacy of povidone-iodine

Large scale trials of the vivo effectiveness of PVP-I are yet to come to provide absolute support for community application.[21] However multiple studies show that using mouthwash, or the gargle method, or as an oral rinse and even delivery via the nasopharynx can reduce viral load.[21,25,32,33,35] Research trials targeting the nose used 0.5% PVP-I with low-dose volume 0.33ml daily consumption. Used as a mouth wash or as a gargle with PVP-I 1% every 2-3 hours or up to 4 times daily was also effective. Most trials were based on positive and suspected individuals infected with SARS-CoV-2, including frontline workers and individuals involved in high-risk work.[21] Studies were not only conducted to evaluate PVP-I effectiveness in the community but also in healthcare settings.[35] Lamas 2020 reported encouraging outcomes with *in vivo* use of PVP-I with 4 Covid-19 positive patients and evaluated its impact on the viral load on the patient's saliva.[30] A study from 2021 by Arefin reported statistically significant outcomes in this domain by conducting research on 189 Covid-19 positive patients.[17] The study was conducted using 0.4%, 0.5%, and 0.6% diluted concentrations of PVP-I nasal irrigation (NI), and 0.5% and 0.6%.for PVP-I nasal spray (NS). Nasopharyngeal clearance was tested after single-time application. The outcome was markedly

significant, both PVP-I NI and NS resulted in potent virucidal clearing against SARS-CoV-2.[25] Another study by Blasi 2021 was reported a COVID-19 patient experience of inhaling 1% PVP-I liquid solution to each nostril until it was felt in the throat. The study also advised the gargles for 60 seconds with the same PVP-I solution, two times a day. These practices led to a consistent reduction in the patient's symptoms.[26] However, not all *in vivo* studies support the use of PVP-I against SARS-CoV-2. Ferrer 2021, did not find any significant reduction in the viral load from saliva samples of COVID-19 positive patients and recommended further larger-scale studies. [33] All *in vivo* model studies have small sample size, but encouraging studies continue to be published supporting the use of *in vivo* PVP against SARS-CoV-2.[32, 35] No side effects were reported among the included studies, and the use of PVP-I was considered safe.

In-vitro Efficacy of povidone-iodine

Most studies were based on *in vitro* effectiveness by using different mouthwashes using SARS-CoV-2 strains against particular epithelial cell lines which are the target site of the virus and the evidence supports its use as a potent disinfectant against SARS-CoV-2, see Table 1. Studies were not just restricted to installation into oral and nasal passages but extended to ocular and dental surgery in recent research.[29,38] All studies reported statistically significant outcomes of incubated cell culture at 37°C and tested the reaction of PVP-I at different time periods.[19, 21] One study using PVP-I disinfection confirmed this as a cost-effective disinfectant during corneal transplants; supporting other promising results where PVP-I was shown to be beneficial against viral transmission.[38] Notably, there was limited interference with other biological substances from PVP-I.[29,34,35] Overall, the *in vitro* studies supported the use of PVP-I topical application as an adjunct to PPE and vaccination or other anti-viral therapeutics used or available in healthcare settings.[31]

Cost-effectiveness of PVP-1 in Covid-19

No study conducted a cost evaluation of PVP-I but some studies reported its cost-effectiveness for reducing mortality and morbidity from SARS-CoV-2[23,24] making it one of the more accessible, safe, simple, and economical options to prevent viral infection both in healthcare and at the self-care community level.[23,24]

Conclusion

This study reviews many aspects of PVP-I efficacy and its application against viral pathogens. Based on the promising outcomes shown *in vitro* and *in vivo*, PVP-I offers a simple nasopharynx and oropharynx viral prevention strategy that is accessible in diverse community settings but also for general healthcare infection control and for ocular and dentistry purposes.[6,23] No oral or nasal study reported any adverse effects such as mucosal irritation, tooth or tongue discoloration, alteration of taste or nasal dysfunction.[6] PVP-I as a mouthwash was reported to be well tolerated, can reduce virus infection, and is easily applicable.[13,16] Because refugees are amongst the most neglected and discriminated population groups in this pandemic, low-cost, accessible, and easy to use antiseptics like PVP-I are expected to contribute to their better health and reduce viral spread within communities.

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Conflicts of interest

The author declares no conflicts of interest.

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