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Hypertonic saline nasal irrigation and gargling should be considered as a treatment option for COVID-19

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Post-hoc secondary analysis of data from our recent Edinburgh and Lothians Viral Intervention Study (ELVIS) pilot randomised controlled trial (RCT) indicates that hypertonic saline nasal irrigation and gargling (HSNIG) reduced the duration of coronavirus upper respiratory tract infection (URTI) by an average of two-and-a-half days. As such, it may offer a potentially safe, effective and scalable intervention in those with Coronavirus Disease-19 (COVID-19) following infection with the betacoronavirus SARS-CoV-2 [1].

ELVIS was undertaken in 66 adults with URTI. Results have been reported in detail elsewhere [2]. Briefly, volunteers with URTI were within 48 hours of symptom onset randomised to intervention (n = 32) or control (n = 34) arms. The intervention arm made hypertonic saline at home and performed HSNIG as many times as needed (maximum of 12 times/day). Control arm participants dealt with their URTI as they normally did. Nose swabs collected at recruitment and first thing in the morning on four consecutive days were sent to the laboratory for testing. Both arms kept a diary (which included the Wisconsin Upper Respiratory Symptom Survey-21 questionnaire) for a maximum of 14 days or until they were well for two consecutive days. Follow-up data were available for 92% of individuals (intervention arm: n = 30; control arm: n = 31). HSNIG reduced the duration of URTI by 1.9 days ($\text{P} = 0.01$), over-the-counter medication use by 36% ($\text{P} = 0.004$), transmission within household contacts by 35% ($\text{P} = 0.006$) and viral shedding by $\geq 0.5 \log_{10}/d$ ($\text{P} = 0.04$) in the intervention arm when compared to controls [2].

We also recently reported that epithelial cells mount an antiviral effect by producing hypochlorous acid (HOCl) from chloride ions [3]. HOCl is the active ingredient in bleach. Epithelial cells have this innate antiviral immune mechanism to clear viral infections. Since bleach is effective against all virus types [4], we tested to see if a range of DNA, RNA, enveloped and non-enveloped viruses were inhibited in the presence of chloride ions supplied via salt (NaCl). All the viruses we tested were: DNA/enveloped: herpes simplex virus; RNA/enveloped: human coronavirus 229E (HCoV-229E), respiratory syncytial virus, influenza A virus; and RNA/non-enveloped: coxsackievirus B3 [3].

In COVID-19, high titres of SARS-CoV-2 are detectable in the upper respiratory tract of asymptomatic and symptomatic individuals [5]. The titres are higher in the nose than the throat suggesting measures that control the infection and viral shedding will help reduce transmission [5]. In the context of the COVID-19 pandemic, these data should be treated with caution, and the intervention should be subjected to further studies to confirm its efficacy and safety.
In the absence of a suitable antiviral agent or a vaccine, we need a safe and effective intervention that can be globally implemented. Our in-vitro data gives the evidence that NaCl has an antiviral effect that works across viral types. The findings from this post-hoc analysis of ELVIS need to be interpreted with caution. These data do however suggest that HSNIG may have a role to play in reducing symptoms and duration of illness in COVID-19.

### Table 1. Number of days for self reported symptom improvement in the control and intervention arms infected by a coronavirus

| Variable label | Treatment   | N  | Mean  | SD   | Difference in mean (INTERVENTION – CONTROL) (95% CI for difference) | P-value |
|----------------|-------------|----|-------|------|---------------------------------------------------------------------|---------|
| Blocked nose   | Intervention| 7  | 4.0   | 2.2  | -3.1 (-6.0, -0.2)                                                   | 0.0362  |
| Blocked nose   | Control     | 8  | 7.1   | 2.9  |                                                                     |         |
| Chest congestion| Intervention| 7  | 1.9   | 1.2  | -0.8 (-2.7, 1.2)                                                   | 0.4056  |
| Chest congestion| Control     | 8  | 2.6   | 2.1  |                                                                     |         |
| Cough          | Intervention| 7  | 2.7   | 1.3  | -3.3 (-5.9, -0.7)                                                   | 0.0179  |
| Cough          | Control     | 8  | 6.0   | 3.0  |                                                                     |         |
| Head congestion| Intervention| 7  | 3.4   | 1.9  | -1.9 (-5.0, 1.1)                                                   | 0.1931  |
| Head congestion| Control     | 8  | 5.4   | 3.3  |                                                                     |         |
| Hoarseness     | Intervention| 7  | 2.9   | 1.6  | -2.9 (-5.6, -0.3)                                                   | 0.0325  |
| Hoarseness     | Control     | 8  | 5.4   | 2.9  |                                                                     |         |
| Scratchy throat| Intervention| 7  | 2.6   | 1.0  | -2.1 (-5.1, 1.0)                                                   | 0.1712  |
| Scratchy throat| Control     | 8  | 4.6   | 3.6  |                                                                     |         |
| Sneezing       | Intervention| 7  | 3.9   | 1.7  | -1.0 (-3.8, 1.8)                                                   | 0.4469  |
| Sneezing       | Control     | 8  | 4.9   | 3.0  |                                                                     |         |
| Sore throat    | Intervention| 7  | 3.6   | 1.9  | -1.1 (-4.4, 2.3)                                                   | 0.5139  |
| Sore throat    | Control     | 8  | 4.6   | 3.7  |                                                                     |         |
| Runny nose     | Intervention| 7  | 4.4   | 1.3  | -1.6 (-4.1, 0.9)                                                   | 0.1999  |
| Runny nose     | Control     | 8  | 6.0   | 2.8  |                                                                     |         |
| Feeling tired  | Intervention| 7  | 3.6   | 1.8  | -2.1 (-5.1, 1.0)                                                   | 0.1671  |
| Feeling tired  | Control     | 8  | 5.6   | 3.3  |                                                                     |         |

SD – standard deviation, CI – confidence interval
Figure 1. Response to global severity question and severity of symptoms. Response from participants over the study period: Each line represents response of a participant over 14 days. Data are shown by treatment group (Top panel – Control Arm; Bottom panel – Intervention Arm). The global severity question was “How unwell do you feel today”. The responses were graded from 0 (Not unwell), 1 (very mildly), 3 (mildly), 5 (moderately) and 7 (severely unwell). Likewise, each symptom was graded 0 (no symptom) to 7 (severe). WURSS-21 Score was the sum of the severity of individual symptoms.
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Authorship contributions: SR conceived the ELVIS trial and was PI on this leading it together with AS. SR, AS and CG planned this post-hoc subgroup analysis. CG was the trial statistician and undertook the secondary analysis. JD managed the virological testing, LM supported with project management expertise. SR and AS jointly drafted the manuscript, which was contributed to by LM and CG. All authors approved the final version of the manuscript.

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