# A pilot, open labelled, RCT of hypertonic saline nasal irrigation and gargling for the common cold

## ELVIS: The Edinburgh and Lothians' Viral Intervention Study

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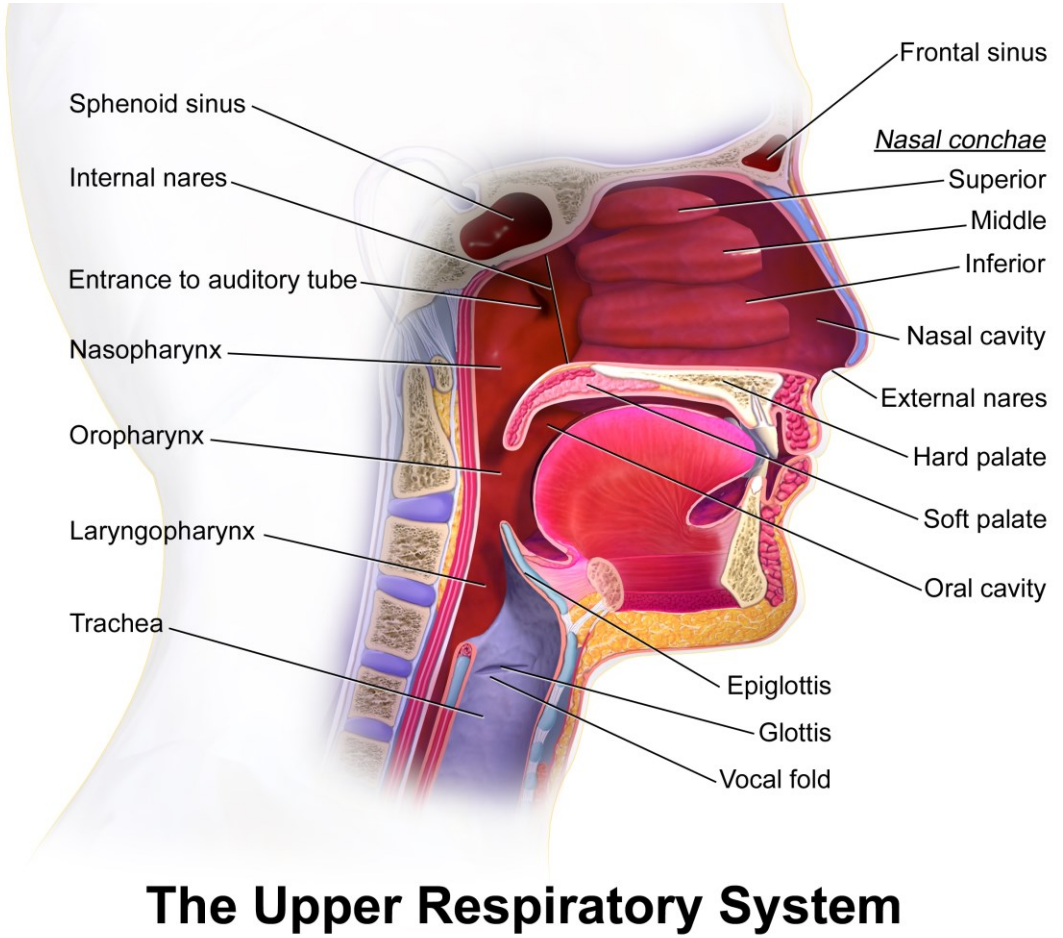
# The need for a generic antiviral

- **The problem:**
  - Many types of viruses cause a common cold
  - There are no antivirals
- **We need a generic antiviral** that works against:
  - DNA / RNA viruses
  - Enveloped / non-enveloped viruses

# The story

- Sore throat
  - Salt water gargles
- ENT surgery:
  - Nasal irrigation with Sodium Bicarbonate
  - Swapped NaCl
- Common cold



The Upper Respiratory System

# Supporting Literature

- Nasal Irrigation for a year in wood workers [1]
  - Reduction in sore throat (p=0.009) & colds (p=0.03)
- Nebulised HTS in Cystic Fibrosis patients (bd) [2]
  - Exacerbations reduced by 56% (P = 0.02)
- Nebulised HTS in Bronchiolitis: Being debated

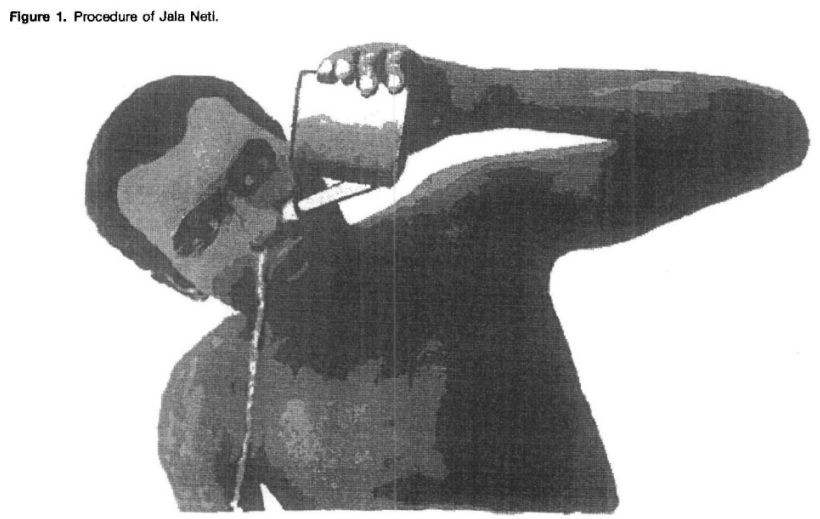


Figure 1. Procedure of Jala Neti.


1. Rabone SJ, et al. Acceptance and effects of nasal lavage in volunteer woodworkers. Occup Med (Lond). 1999 Aug;49(6):365-9.
2. Elkins M. R. et al. A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis. N Engl J Med 2006;354:229-40.

# Effect of salts on Mengo virus

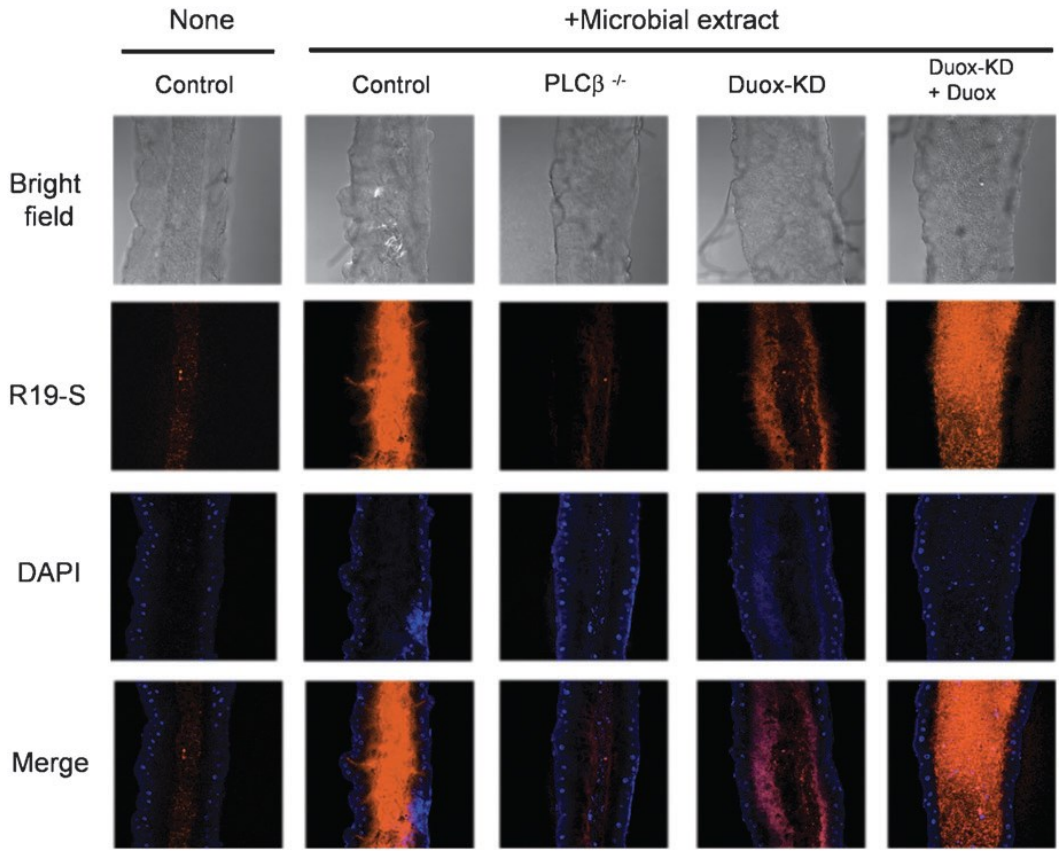
| Diff. Sodium Salts | | |
|---|---|---|
| **Diluent (150mM)** | **Virus $LD_{50}$ $-\log_{10}$** | |
| | **0'** | **120'** |
| NaCl | 7.7 | 3.5 |
| $NaClO_4$ | 8.4 | 7.5 |
| $NaNO_3$ | 8.7 | 7.8 |
| $NaH_2PO_4$ | 7.5 | 6.5 |
| $Na_2HPO_4$ | 7.8 | 7.1 |
| $Na_2SO_4$ | 7.8 | 7.2 |
| Na formate | 8.2 | 6.8 |
| Na acetate | 7.8 | 6.5 |
| DW | 8.3 | 7.5 |

| Diff. Chloride Salts | | |
|---|---|---|
| **Diluent** | **Virus $LD_{50}$ $-\log_{10}$** | |
| | **0'** | **120'** |
| NaCl (150mM) | 7.7 | 3.4 |
| KCl (150mM) | 8.0 | 3.5 |
| $MgCl_2$ (75mM) | 7.8 | 3.5 |
| $CaCl_2$ (75mM) | 7.1 | 3.5 |
| DW | 8.3 | 7.8 |

| Diff. Halide Salts | | |
|---|---|---|
| **Diluent (150mM)** | **Virus $LD_{50}$ $-\log_{10}$** | |
| | **0'** | **120'** |
| NaF | 8.3 | 7.4 |
| NaCl | 7.8 | 3.5 |
| NaBr | 7.6 | 3.6 |
| NaI | 7.7 | 4.5 |
| NaSCN | 7.0 | 6.5 |
| DW | 8.2 | 7.6 |

*Spier RW. Exp Biol Med (Maywood) February 1961 vol. 106 no. 2402-404*

# Fruit fly: Gut epithelial cells produce HOCl



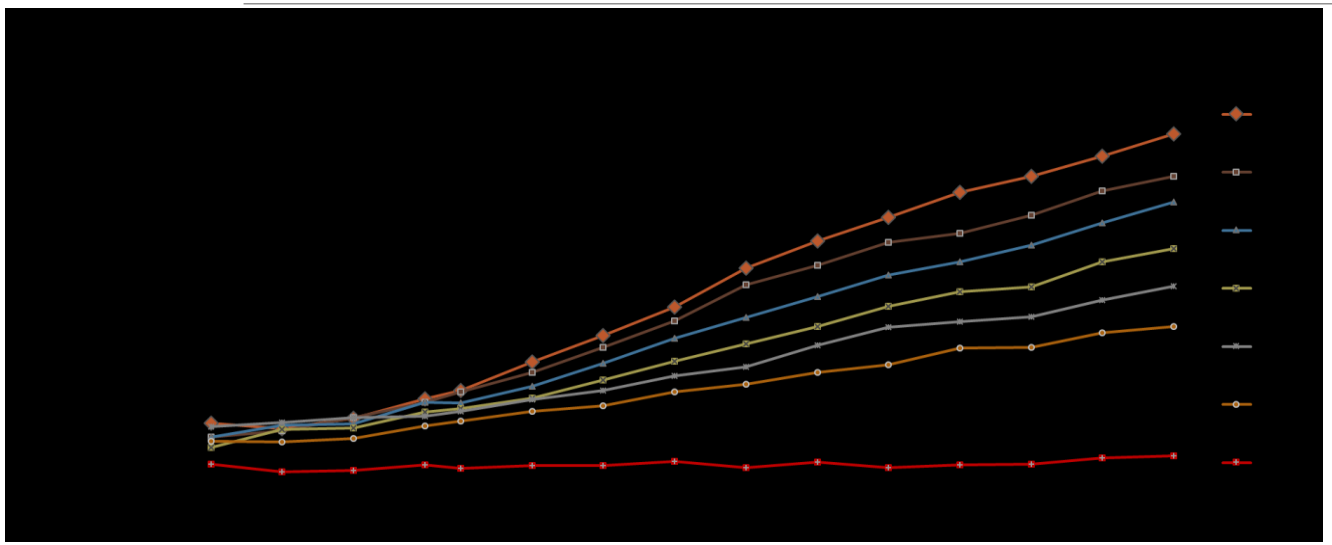

Chen X et al. Chem. Commun., 2011, **47, 4373–4375**

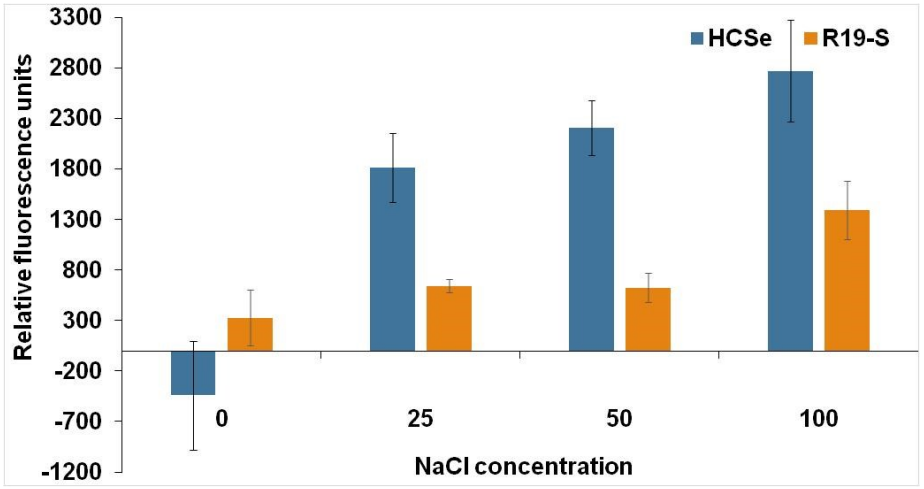
- They took some bacteria and ground it up and added sugar to it.
- Fruit fly were fed the sweet solution containing the bacterial lysate
- An hour later they cut open the fruit fly and stained the gut epithelium for HOCl
- Bottom Right – Gut epithelial cells are fluorescing (i.e. producing HOCl)
- HOCl is the active ingredient in bleach!

# Hypothesis

- Chloride salts (e.g. NaCl) can help suppress viral infection
- The suppression is mediated through increased HOCl production
- This antiviral mechanism can be used by the cell against different viruses

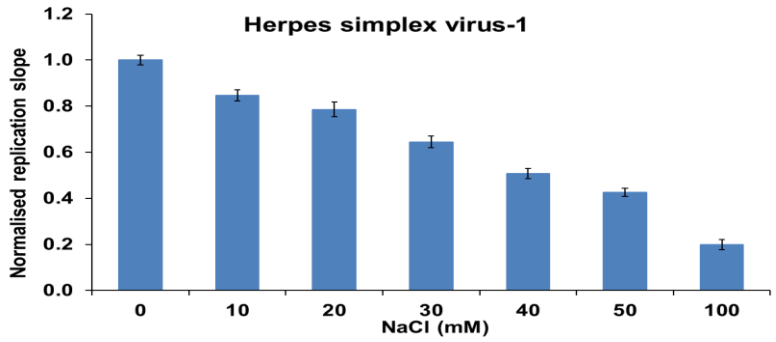
# Effect of NaCl on eGFP HSV-1 in HeLa Cells

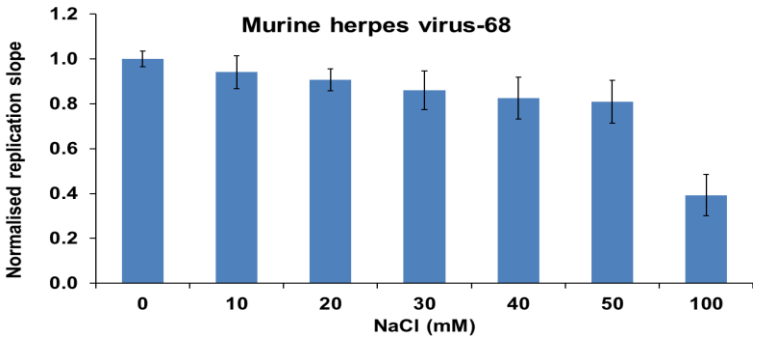


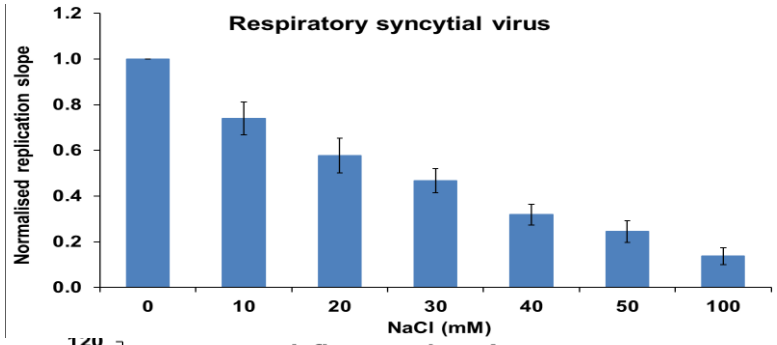


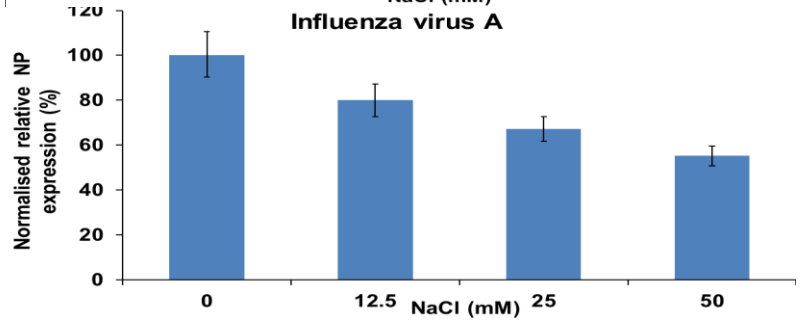

- Dose dependent reduction in viral replication
- HOCl production (as early as 2 hours)

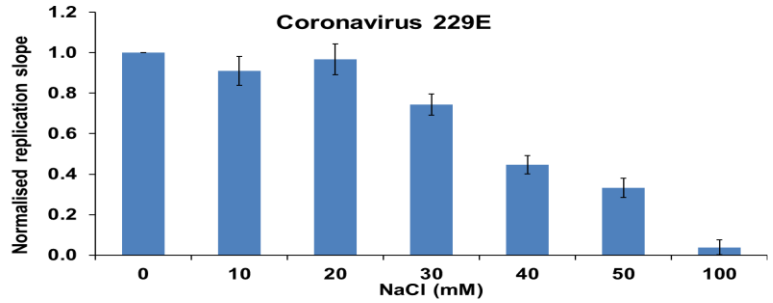
# DNA/RNA; enveloped/non-enveloped viruses inhibited:

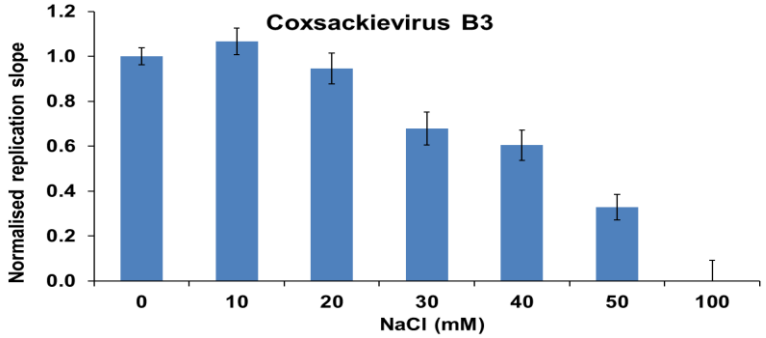


# Summary

- NaCl has a dose-dependent antiviral effect
- Antiviral effect is
  - Intracellular
  - Needs Chloride ion
  - $Cl^-$ is converted to HOCl
  - If you block conversion of $Cl^-$ to HOCl, viral inhibition is reversed
- **Chloride salts can be a therapeutic antiviral agent**

# ELVIS: Aim & Outcome Measures

**Primary outcome measure:** What is the recruitment rate?

**Secondary outcome measures:**

- Compliance
- Acceptability
- Difference in duration of symptoms
- Difference in viral shedding

# Sample Size

- Maximum of 80 participants
- Aimed to get feedback from ~30 participants / arm

- 27 per group:  Can express proportion of those who return the symptom score diary & samples to within ±19%
- Based on a two-sided 95% CI around an expected proportion of 0.5
- Two groups combined (n= 54):  Able to express proportion to within ±13%
- Allow for 10% dropouts: Sample size was increased to 30/arm

# Inclusion

- **>16 years**
- URTI **<48 hours** of onset
- **Yes to:**
  - Do you have a cold? Or
  - Do you think you are coming down with a cold?
- **AND** Jackson Score of ≥2

1. Nasal discharge
2. Nasal obstruction
3. Sneezing
4. Sore throat
5. Headache
6. Malaise
7. Chilliness
8. Cough

At least one of the first four symptoms

# Exclusion

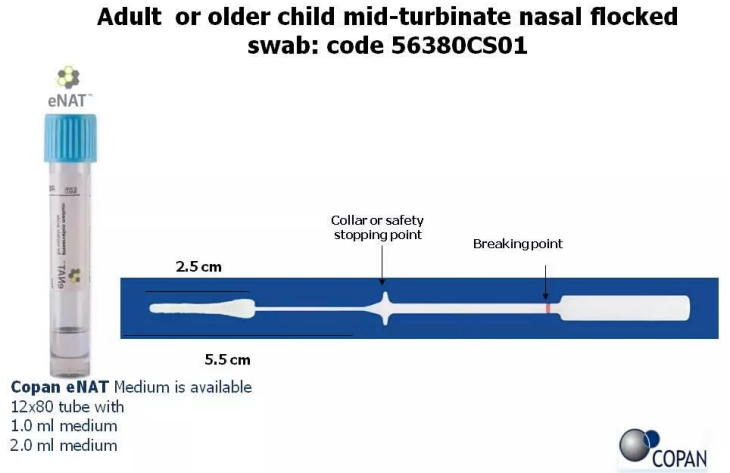
- URTI >48 hours
- On antibiotics
- Pregnant
- Chronic conditions
- Immunosuppressed
- Allergic rhinitis

  H/o allergy +

  eye/nose itching or sneezing
- Unable to perform HSNIG
- Taking part in another medical trial

# Both Groups

- **Consented & Randomisation (online):**
  - Minimisation by **Sex** and **Smoking Status**
- **Taught:**
  - **To fill daily form (paper / online): (Max 14 days / until well for 2 days)**
    - Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS-21)
    - EQ-5D-5L Quality of Life
  - **Mid-Turbinate Swabs in eNAT medium (Copan, Italia):**
    - Shown a video
    - Baseline + 4 subsequent days
    - Specimen posted with Royal Mail Safeboxes
- **Allowed over the counter medication**

# Daily Forms: Based on WURSS-21
## (2x"not unwell" OR 14 days max)

Edinburgh and Lothians Viral Intervention Study

Subject Number: _____ Date: Time:

**Daily Form – Day 1**

| | Not unwell 0 | Very Mildly 1 | 2 | Mildly 3 | 4 | Moderately 5 | 6 | Severely 7 |
|---|---|---|---|---|---|---|---|---|
| 1 How unwell do you feel today? | O | O | O | O | O | O | O | O |

Once you have answered 'not unwell' for 2 consecutive days or for a maximum of 14 days you do not need to complete any further information on the daily form. Please go directly to the 'End of study form'.

2. Please rate the average severity of your cold symptoms over the last 24 hours for each symptom

| | Do not have this 0 | Very Mildly 1 | 2 | Mildly 3 | 4 | Moderately 5 | 6 | Severely 7 |
|---|---|---|---|---|---|---|---|---|
| Runny nose | O | O | O | O | O | O | O | O |
| Blocked (plugged) nose | O | O | O | O | O | O | O | O |
| Sneezing | O | O | O | O | O | O | O | O |
| Sore throat | O | O | O | O | O | O | O | O |
| Scratchy throat | O | O | O | O | O | O | O | O |
| Cough | O | O | O | O | O | O | O | O |
| Hoarseness | O | O | O | O | O | O | O | O |
| Head congestion | O | O | O | O | O | O | O | O |
| Chest congestion | O | O | O | O | O | O | O | O |
| Feeling tired | O | O | O | O | O | O | O | O |

3. Over the last 24 hours, how much has your cold interfered with your ability to:

| | Not at all 0 | Very Mildly 1 | 2 | Mildly 3 | 4 | Moderately 5 | 6 | Severely 7 |
|---|---|---|---|---|---|---|---|---|
| Think clearly | O | O | O | O | O | O | O | O |
| Sleep well | O | O | O | O | O | O | O | O |
| Breathe easily | O | O | O | O | O | O | O | O |
| Walk, climb stairs, exercise | O | O | O | O | O | O | O | O |
| Accomplish daily activities | O | O | O | O | O | O | O | O |
| Work outside the home | O | O | O | O | O | O | O | O |
| Work inside the home | O | O | O | O | O | O | O | O |
| Interact with others | O | O | O | O | O | O | O | O |
| Live your personal life | O | O | O | O | O | O | O | O |

4. Compared to yesterday, I feel that my cold is:

| Very much better | Somewhat better | A little better | The same | A little worse | Somewhat worse | Very much worse |
|---|---|---|---|---|---|---|
| O | O | O | O | O | O | O |



Edinburgh and Lothians Viral Intervention Study

Subject Number: _____ Date: Time:

**Daily Form – Day 1**

Procedure – **All:**

5.a. Please note you are allowed to either blow or not blow your nose before nasal swab is collected. We just need to know the procedure you followed.

Did you collect nasal swab? Yes O No O

If Yes: Did you blow your nose prior to collecting nasal swab? Yes O No O

Procedure – **Intervention arm only**, controls please go to Q9.

5.b. If you performed the nasal irrigation procedure yesterday did you use the same concentration of solution? Yes O No O Did not perform yesterday O

If yes please go to Q6, if not:

How much salt have you used? _____.____ grams

How much water have you used? _____.____ ml

6. How many times have you performed the procedure in the last 24 hours?

0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 O 11 O 12 O

7. What techniques did you use?

Irrigation + gargle O

Irrigation only O

Gargle only O

None O

If none please indicate reason: _____

8. Did you notice any side effects? Yes O No O

If yes please indicate how severe you felt these:

| | None 0 | 1 | 2 | 3 | 4 | Severe 5 |
|---|---|---|---|---|---|---|
| Irritation | O | O | O | O | O | O |
| Burning | O | O | O | O | O | O |
| Pain | O | O | O | O | O | O |
| Dryness | O | O | O | O | O | O |
| Runny nose | O | O | O | O | O | O |
| Other | O | O | O | O | O | O |
| If other please describe: | | | | | | |

9. Since you last completed these questions have you taken any cold / flu related medications? Yes O No O

If yes, what did you take? _____



Edinburgh and Lothians Viral Intervention Study

Subject Number: _____ Date: Time:

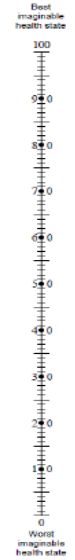
**Daily Form – Day 1**

10.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own health state today**




11. Since you last completed these questions have you sought further medical attention for your cold?

Yes O No O

If yes where did you seek help?

GP O

Hospital O

Other O please specify: _____

_____

(If you have answered Yes to this question, please go to the "End of study form")

# Intervention Arm


- **Taught:** ([WWW.ELVISSTUDY.COM](http://WWW.ELVISSTUDY.COM))
  - To prepare hypertonic saline solution
  - To perform Nasal Irrigation and Gargling
    - Number of times: Depending on symptoms

Amount of Salt in grams to be added to make different volumes of solution
Bowl - Choose the size that you find convenient.

| | Concentration of solution | | | |
|---|---|---|---|---|
| Add g of salt to make solution | 3.0% | 2.5% | 2.0% | 1.5% |
| 100ml – Bowl | 3g | 2.5g | 2g | 1.5g |
| 200ml – Bowl | 6g | 5g | 4g | 3g |
| 500ml – Flask | 15g | 12.5g | 10g | 7.5g |

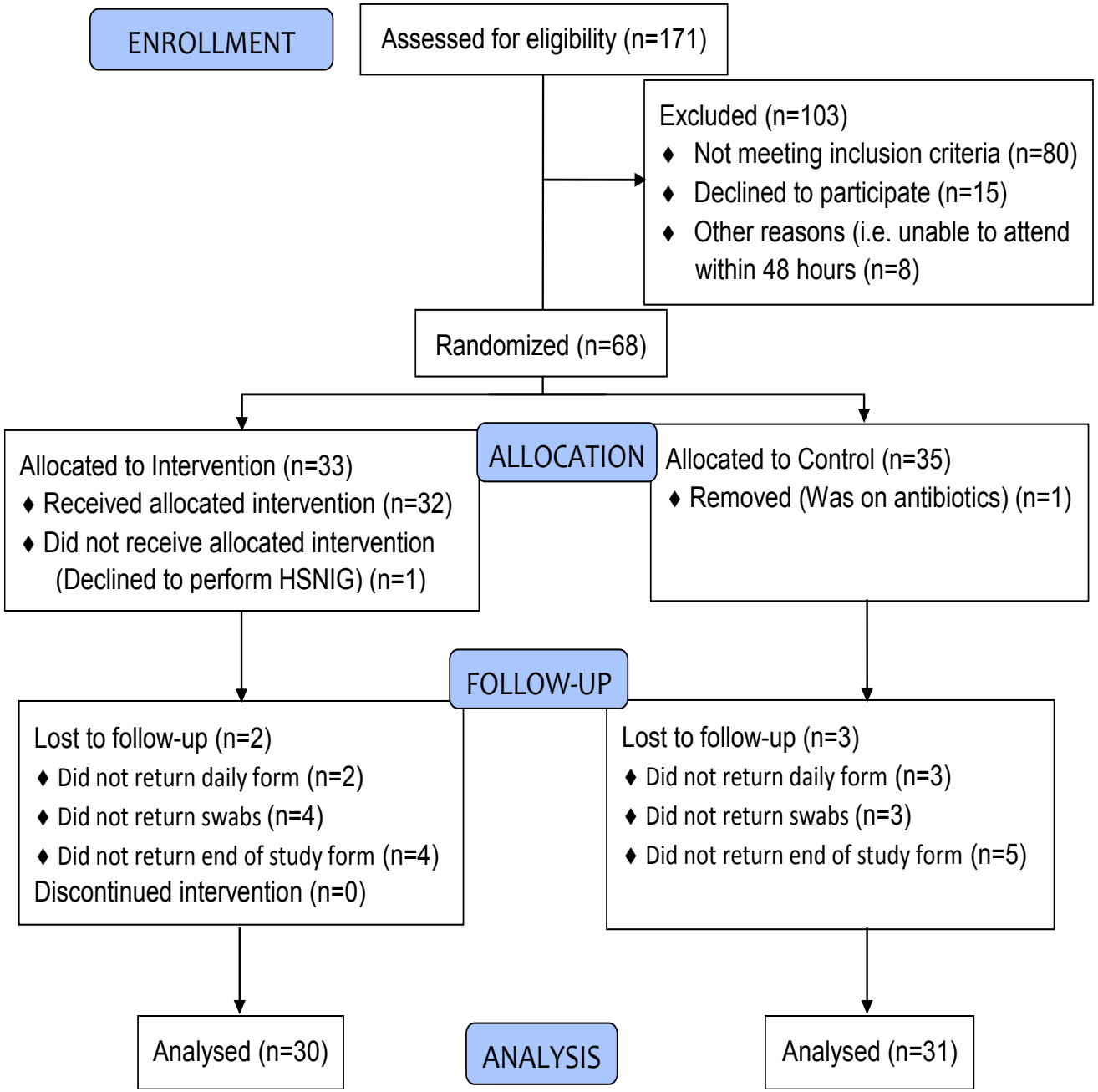
# How to prepare and perform HSNIG:

Please visit

http://www.elvisstudy.com/nasal-irrigation-and-gargling.html

for instructions and videos.

# CONSORT 2010 Flow Diagram



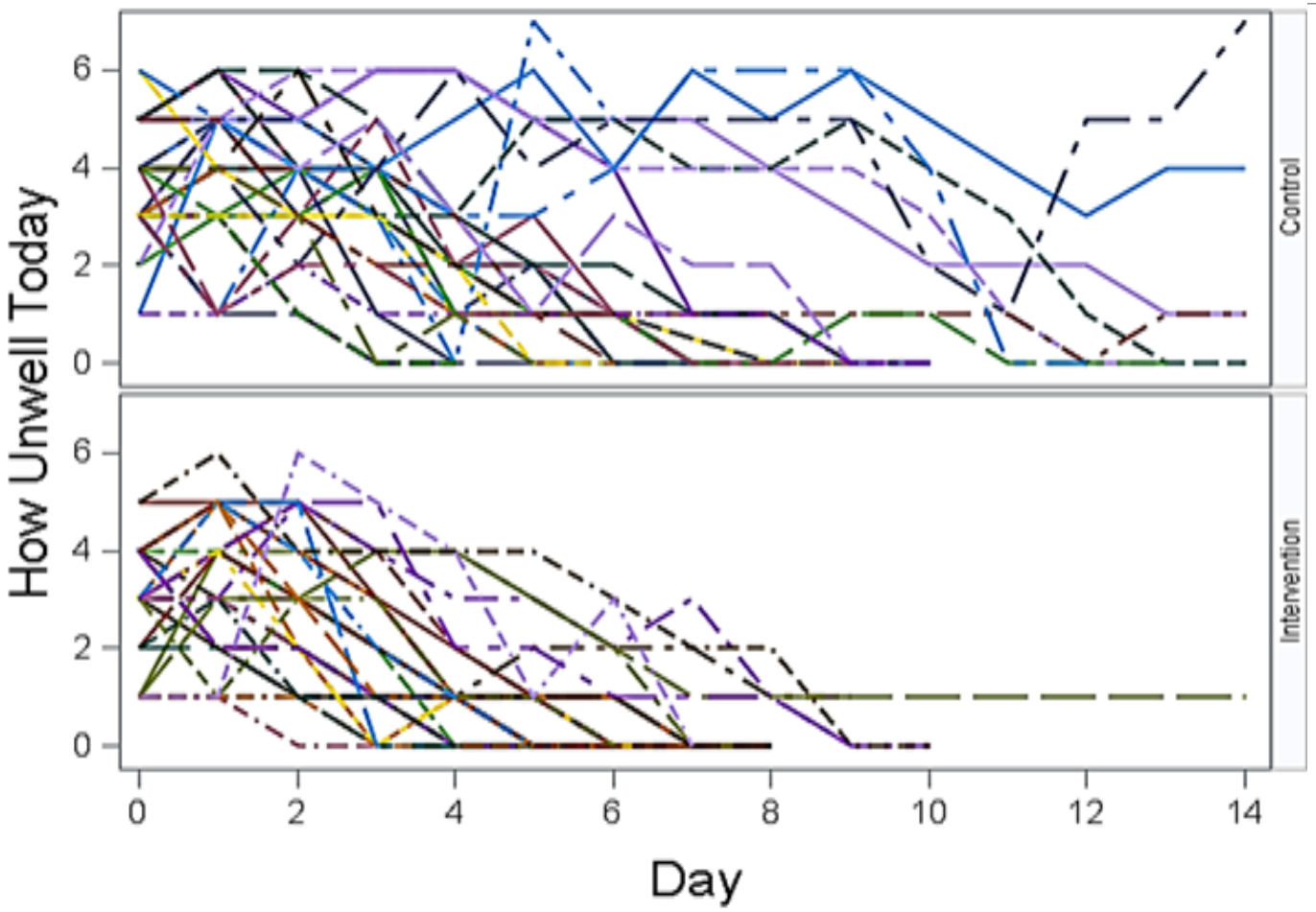
# Baseline Characteristics Similar

| | Intervention | | Control | |
|---|---|---|---|---|
| | n | % | n | % |
| Randomised | 32 | 100 | 34 | 100 |
| Sex - F | 24 | 75 | 25 | 74 |
| Non/Ex-Smokers | 31 | 97 | 31 | 91 |
| >1 adults at home | 26 | 81 | 29 | 85 |
| No kids at home | 19 | 59 | 19 | 56 |
| Nobody sick before them | 19 | 59 | 21 | 62 |
| Full time employment | 20 | 63 | 21 | 62 |
| Part time employment | 7 | 22 | 5 | 15 |
| Full time education | 4 | 13 | 4 | 12 |

| | Intervention | | Control | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age | 34.6 | 9.3 | 39.4 | 10.9 |
| WURSS-21 Scot Score | 65.9 | 13.6 | 63.7 | 17.4 |
| EQ-VAS (QoL score) | 41.6 | 18.2 | 43.9 | 21.8 |

| Preference | % |
|---|---|
| **Feedback** | |
| **Paper** / Online | **75** / 25 |
| **Hypertonic saline concentration** | |
| **3.0%** / 2.5% /2.0% | **81** / 9 / 9 |

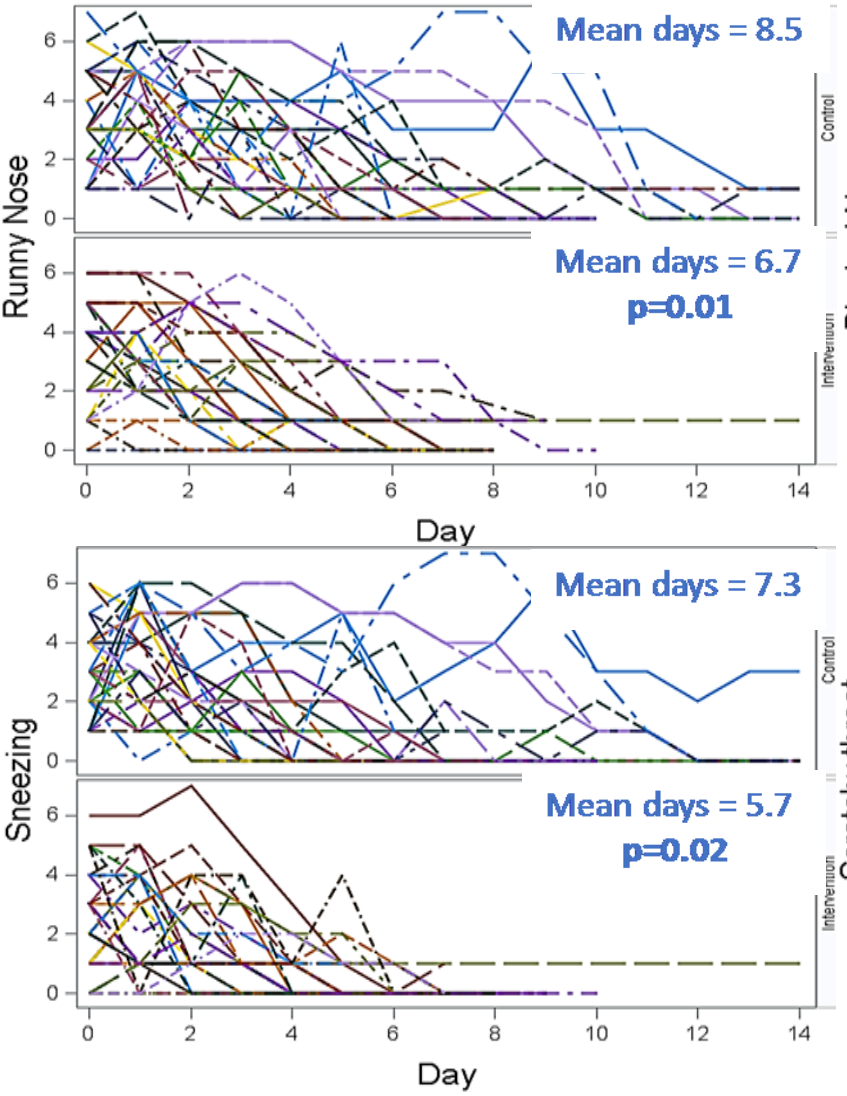
# Intervention arm: Well **2 days** earlier:

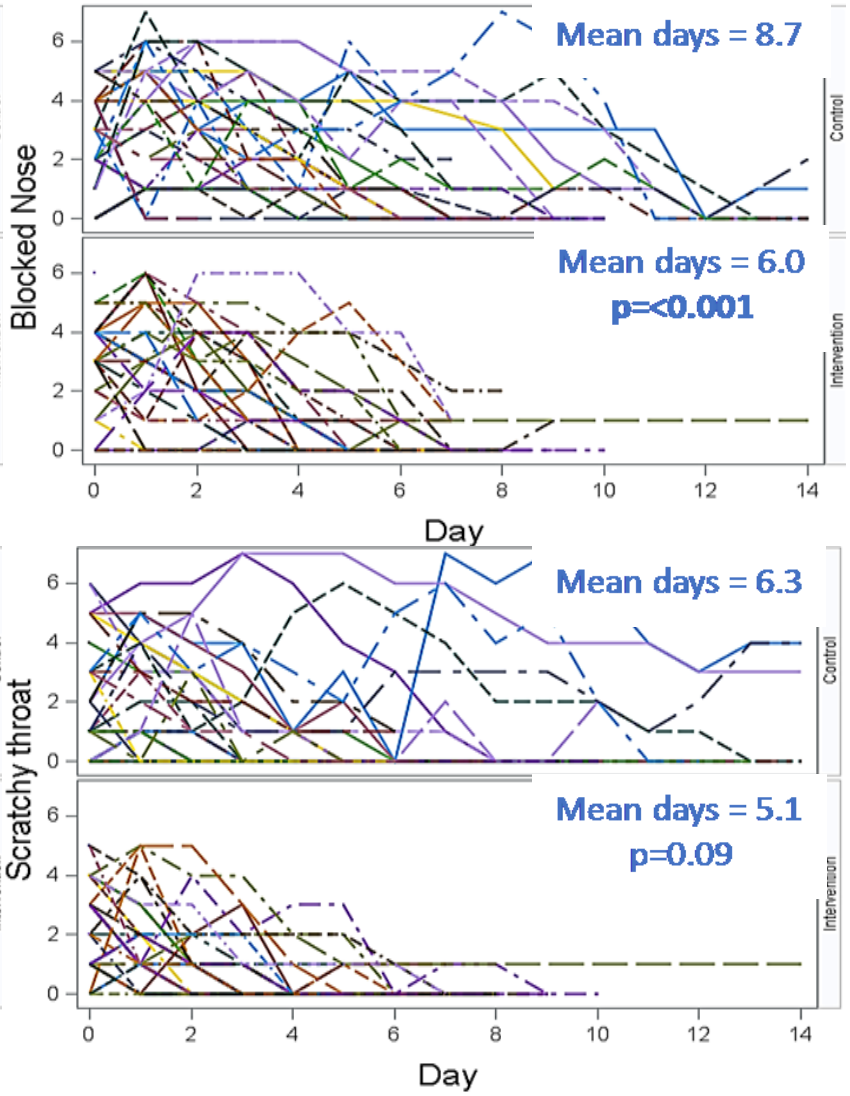


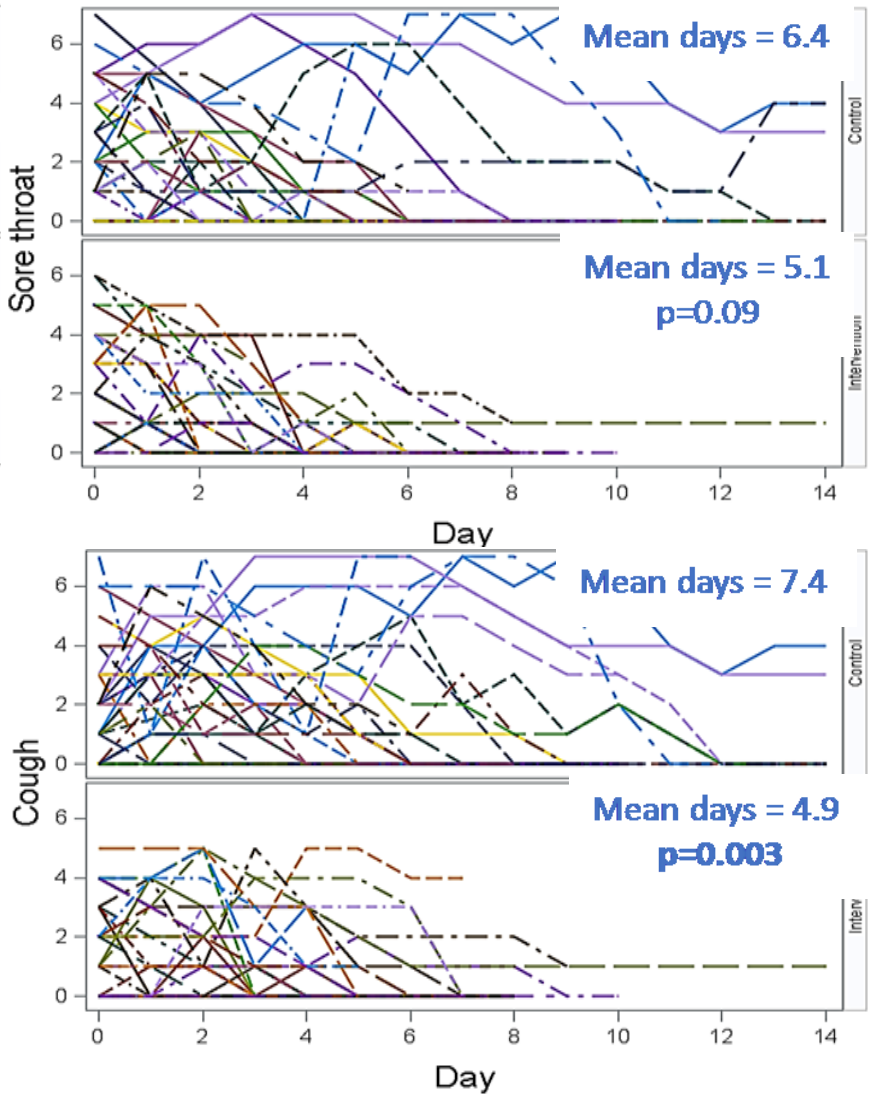

- Diary from 61 participants
  - 5 – Did not reach end point on day 14
  - 11 – Stopped before scoring 0 for 2 days
    - 8 – Scored 0 on last day
    - 2 – Scored 1 on last day
    - 1 – Scored 6 on last day

| | Intervention n=30 | | Control n=31 | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Days | **6.8** | 2.2 | **8.7** | 3.3 | **0.012** |

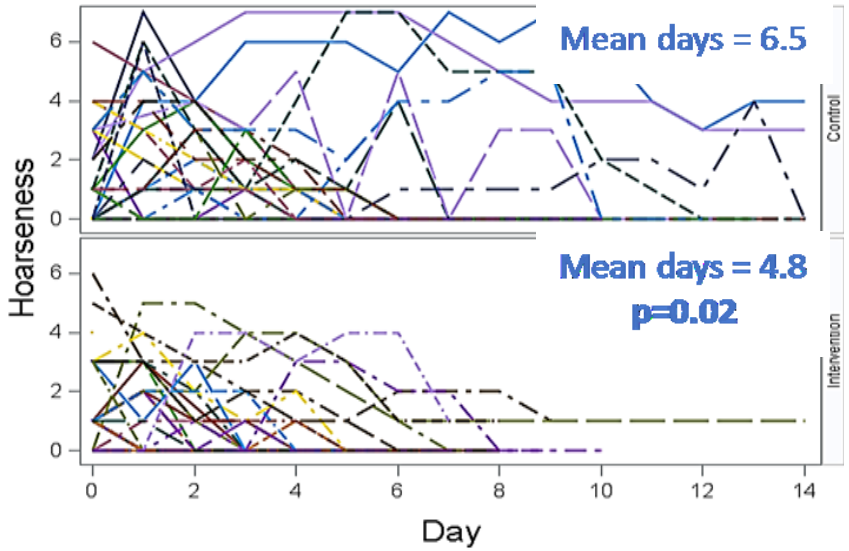
# Days to clear symptoms:

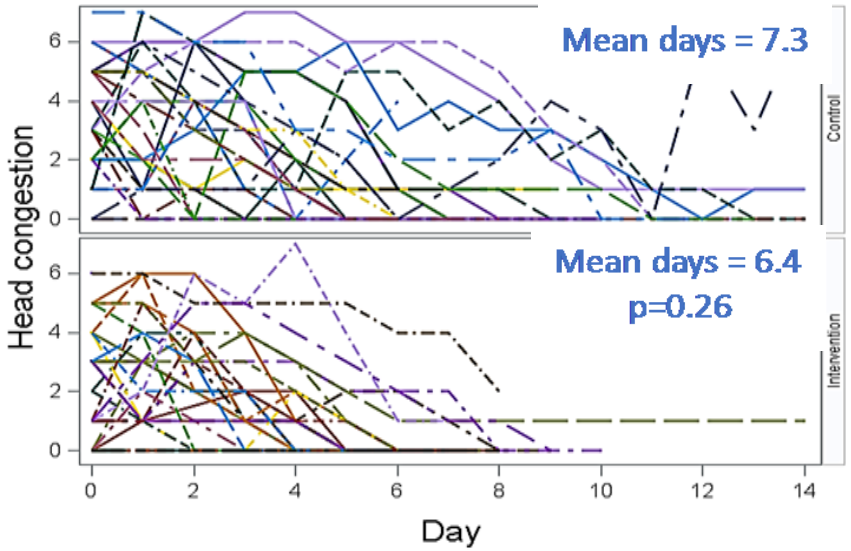


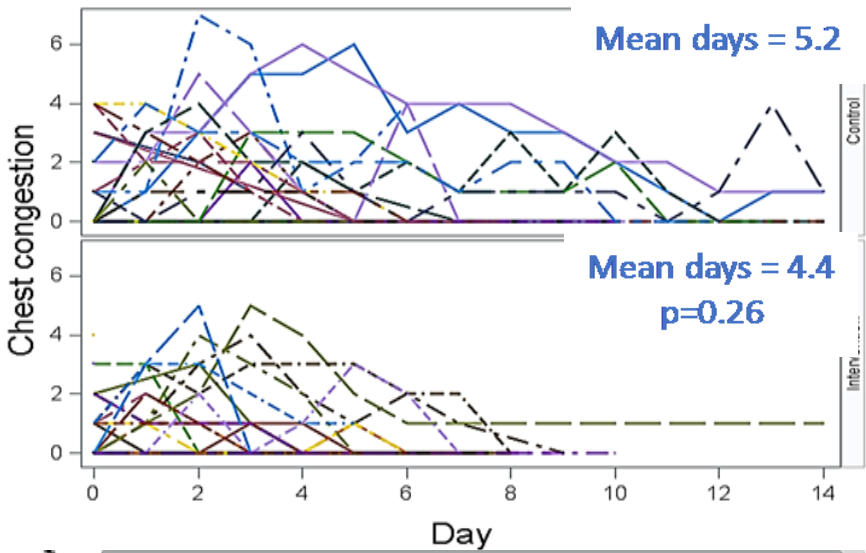



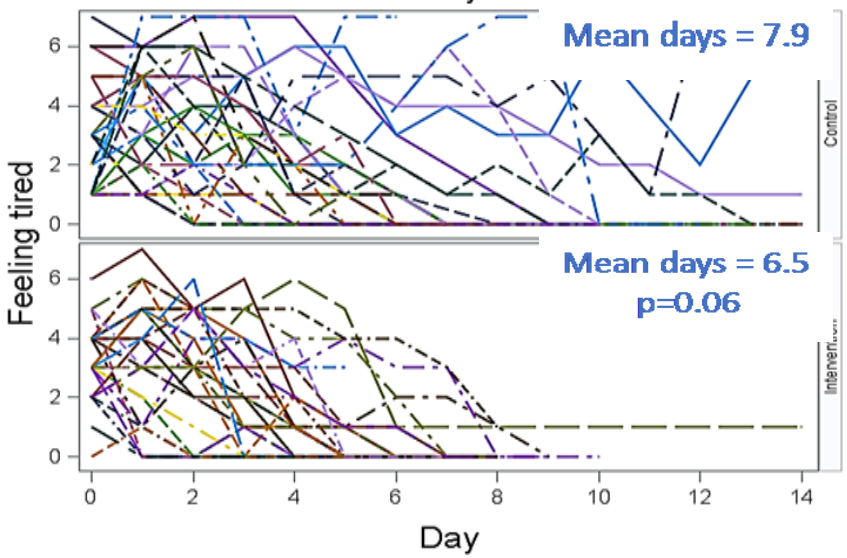



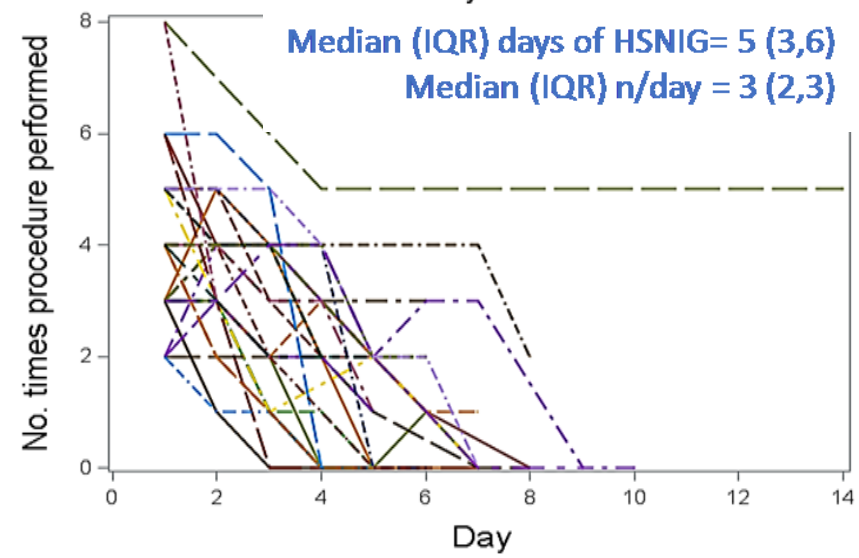
# Days to clear symptoms:

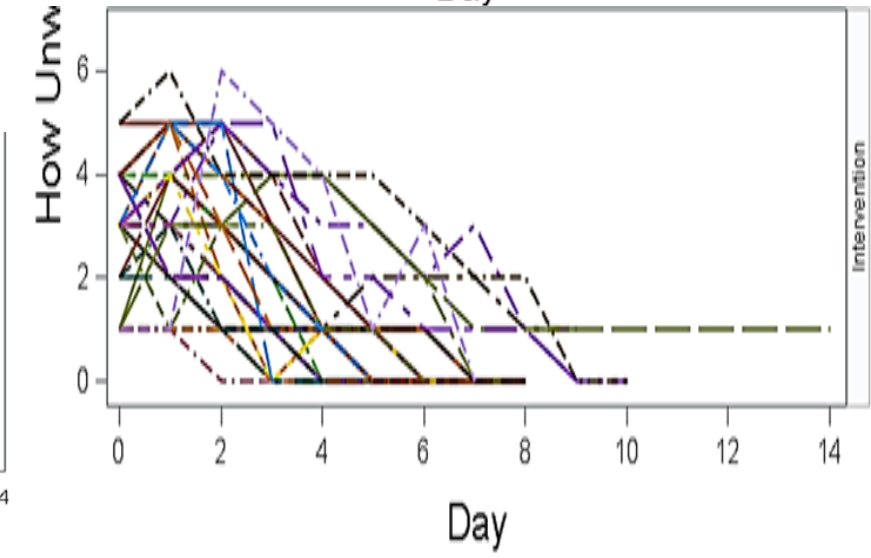


# Feedback from participants

| | Intervention | | Control | | p |
|---|---|---|---|---|---|
| | n=28 | % | n=29 | % | |
| Time off work | 3 | 11 | 7 | 24 | |
| 3 days off work | 0 | 0 | 4 | 14 | |
| **Medication** for URTI | 14 | **50** | 25 | **86** | **0.004** |
| **Symptoms after participant** | 8 | **31** | 19 | **66** | **0.005** |

# HSNIG – Feedback:

| | | n=28 | % |
|---|---|---|---|
| **Preparation of solution** | Flask | 24 | 86 |
| | **Easy** | 28 | **100** |
| **Procedure** | Small bowl | 21 | 75 |
| | **Comfortable** | 11 | **39** |
| | **Moderately comfortable** | 14 | **50** |
| Cleaning | Easy | 27 | 96 |
| **Outside home** | **Easy** | 8 | 28 |
| | **Moderately Easy** | 11 | 39 |
| Carrying | Easy | 16 | 57 |
| | Moderately easy | 7 | 25 |
| **On the whole** | **Convenient** | 11 | **40** |
| | **Moderately convenient** | 14 | **50** |

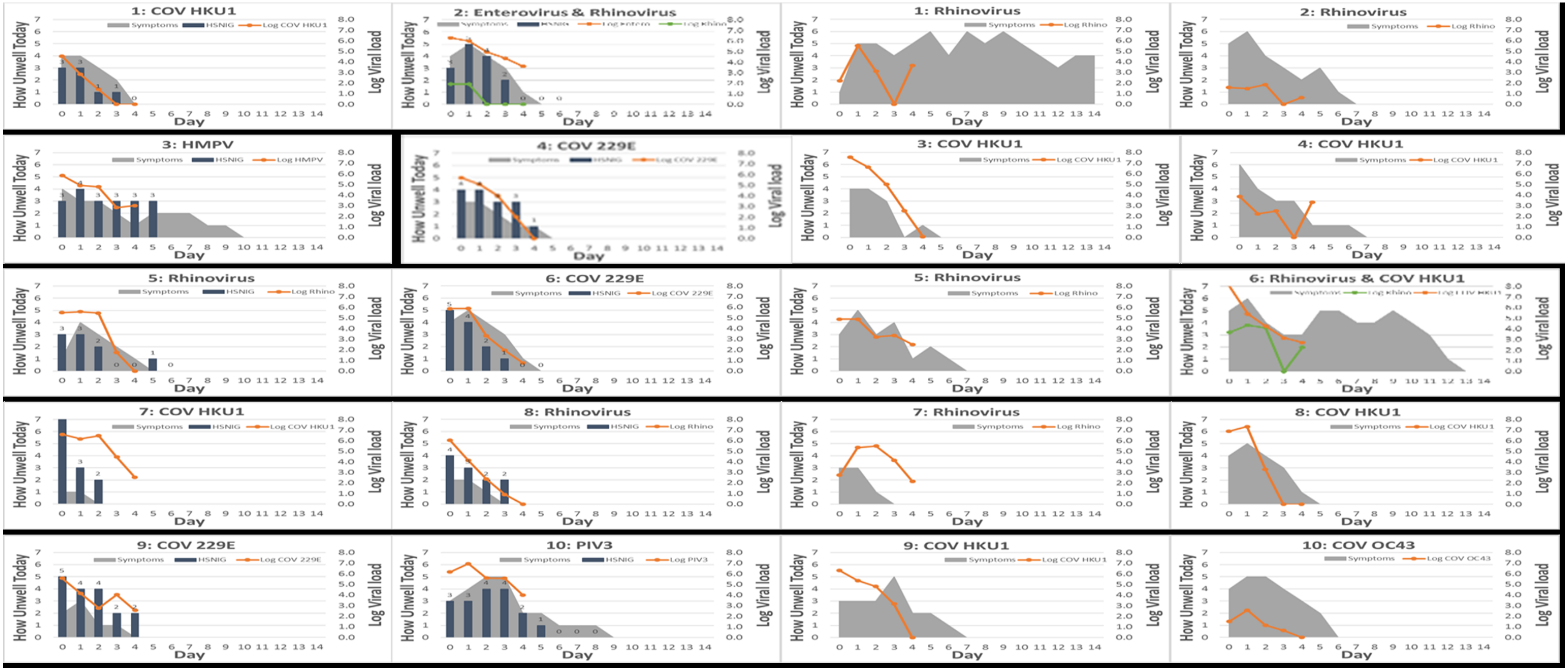
| | | n=28 | % |
|---|---|---|---|
| **Did HSNIG make a difference** | **Yes** | 26 | **93** |
| **Will you use procedure?** | **Likely** | 17 | **61** |
| | Undecided | 7 | 25 |
| | Unlikely | 4 | 15 |
| If more convenient | Likely | 24 | 86 |
| | Undecided | 2 | 7 |
| | Unlikely | 2 | 7 |
| As a preventative measure | Likely | 6 | 21 |
| | Undecided | 2 | 7 |
| | Unlikely | 20 | 72 |

# Virology

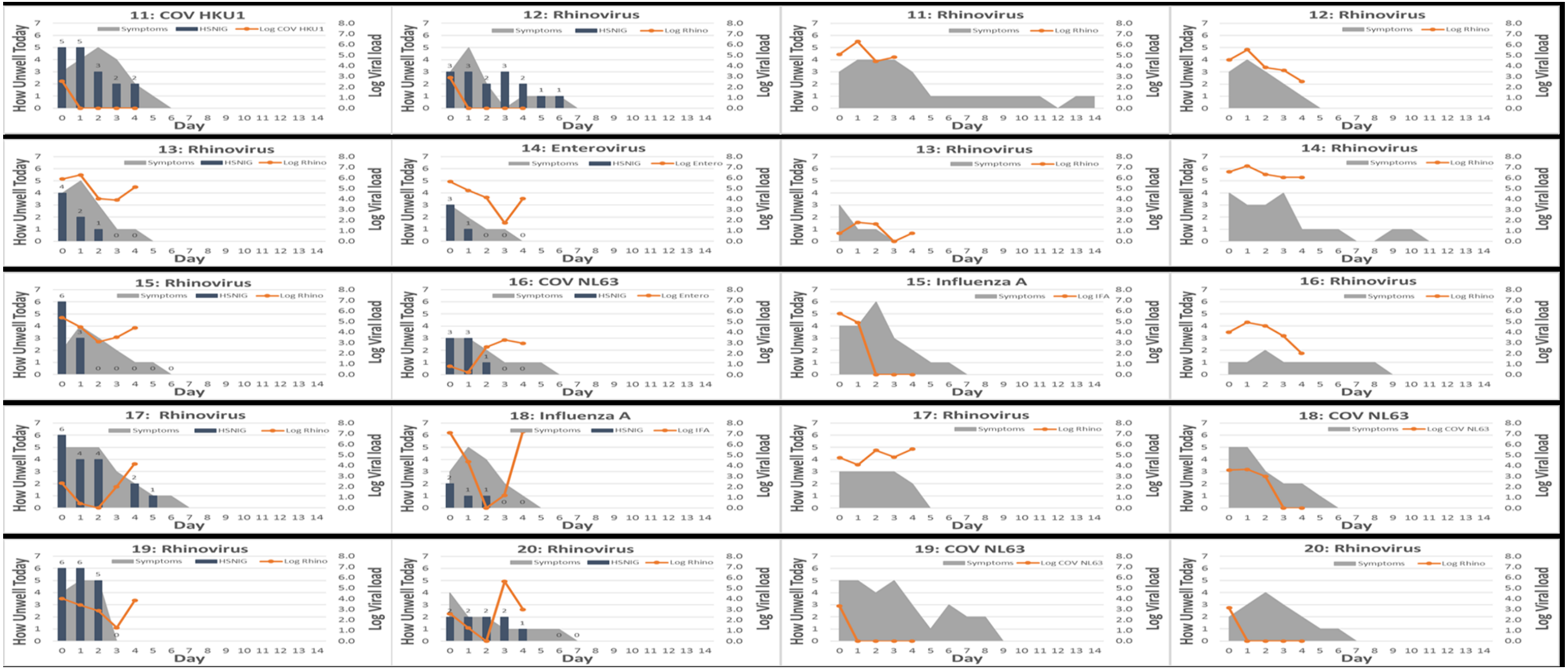
- 18 – No virus identified
- 44 – One virus
- 4 – Two viruses identified
  - 3 – Rhinovirus + enterovirus,
    - 1 – Confirmed
    - 1 – No followup
  - 1 – Rhinovirus + Coronavirus OC43

| | Intervention | | Control | |
|---|---|---|---|---|
| | n=32 | % | n=34 | % |
| Rhinovirus | 15 | 47 | 13 | 38 |
| All Coronaviruses | 7 | 22 | 8 | 24 |
| Coronavirus 229E | 3 | 9 | 0 | 0 |
| Coronavirus OC43 | 0 | 0 | 1 | 3 |
| Coronavirus HKU1 | 3 | 9 | 5 | 15 |
| Coronavirus NL63 | 1 | 3 | 2 | 6 |
| Influenza A | 1 | 3 | 1 | 3 |
| Respiratory syncytial virus | 1 | 3 | 1 | 3 |
| Parainfluenza virus-3 | 2 | 6 | 0 | 0 |
| Enterovirus | 2 | 6 | 1 | 3 |

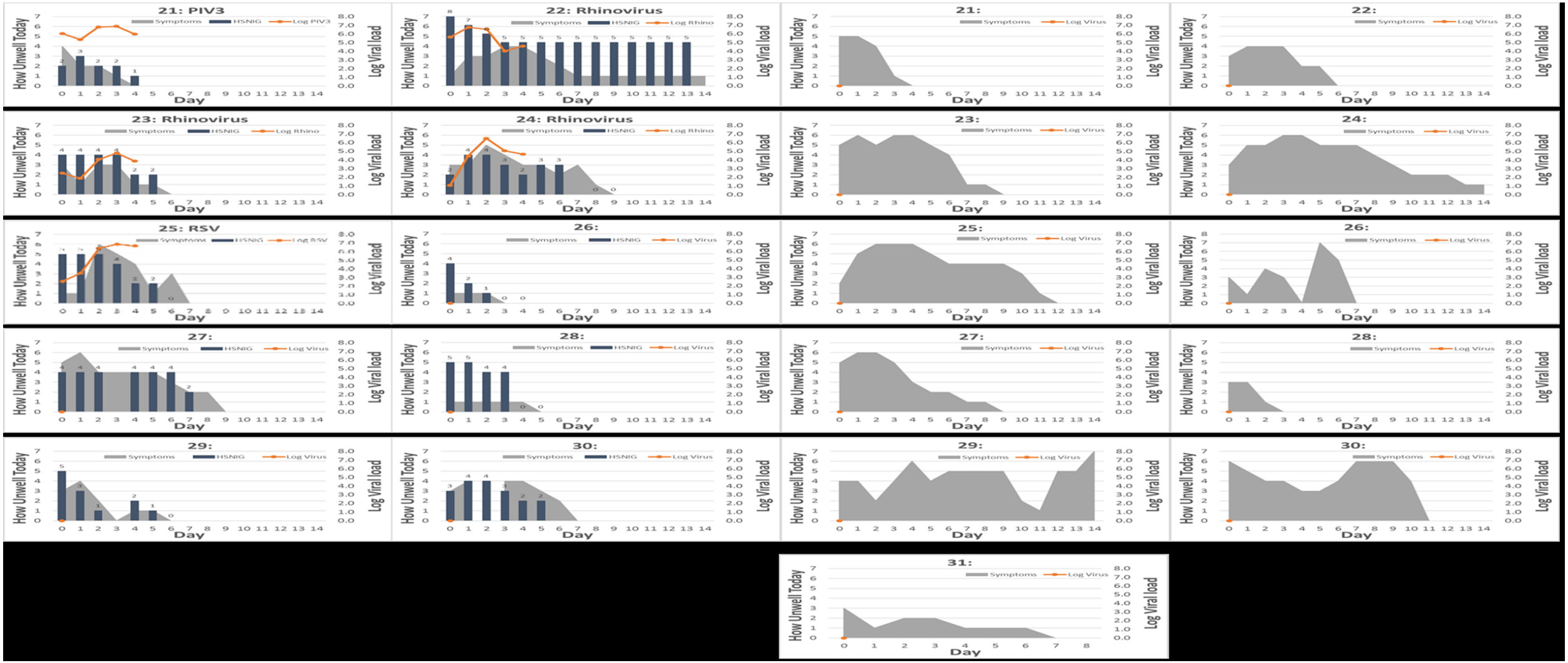
# Symptoms, Irrigation Vs Viral shedding:



# Symptoms, Irrigation Vs Viral shedding:



# Symptoms, Irrigation Vs Viral shedding:



# Reduction in Viral Shedding:

- The mean inter-assay variation for the Day 0 sample was 0.21 $\log_{10}$ (SD = 1.17)
  - A reducing trend in viral shedding was seen on days HSNIG was done in 20 individuals.
  - Among these viral shedding increased after HSNIG was stopped in 8/20 (40%)
  - Two participants restarted HSNIG (1 with an increase in viral shedding)

- **Fall in viral shedding by ≥0.5 log10/day:**
  - Intervention arm 73% [n=16/22]
  - Control arm 43% [n=9/21]
  - Difference -30%, 95% CI for difference in proportion (-58, -2) **(p=0.038)**

# Conclusions:

| Outcome measures | Our findings |
|---|---|
| Are we able to **recruit and retain participants**? | Yes |
| Is **procedure acceptable**? | Yes |
| Is there a difference in the **quality of life**? | **Less Medication** |
| **Is there a Reduction in Duration of symptoms?** | **By 2 days** |
| Is there a **Reduction in Viral Shedding**? | **Yes + Less transmission** |

**<u>Time for a larger study with efficacy end points</u>**

# ELVIS Kids in children (n=480):


# Acknowledgements - ELVIS


**Edinburgh and Lothians Health Foundation**

**Edinburgh Council**

**Midlothian Council**

**Clinical Research Facility Staff** :

Audrey Kuchnowsky, Jill Steven and team

**Ethics Committee**

**Lothian GP's**

**Participants**

**Colleagues:** Aziz Sheikh, Catriona Graham and Lynn Morrice

**Prof. Bruce Barrett** – Permission to use WURSS-21

**Cornish Sea Salt** – Philip Tanswell

**Copan Italia** – Santina Castriciano

**Butterfly Films** - Ryan

**Edinburgh Clinical Trials Unit** – Allan Walker and David Buchanan

**NHS Lothian:**

**R&D Department** – Susan Shepherd

**Department of Virology** – Jenny Dove and Julie White

**Finance Department** – Glen Merritt

**Communications -** Clifford Burden