# Collecting clinical experience of homeopathic support in COVID-19, newsletter 14

## Bayesian analysis of symptoms, 13th issue

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The previous newsletter about Bayesian analysis of symptoms discussed **causality**, did the homeopathic medicine really cause the improvement? Every doctor underestimates the influence of the placebo-effect; together with spontaneous recovery this might be responsible for more than half of all cures. These so-called 'false positive cases' cause underestimation of the likelihood ratio (LR) of a specific symptom for a specific medicine. The prevalence of a symptom in the false positive medicine population is, in fact, the same as in the remainder of the population.

In this newsletter we discuss another source of underestimation of LR: lowering the **cut-off value for a symptom**. An example: the symptom 'cough' can be called positive if the patient coughs every minute, or only once a day. It is self-evident that the lower cut-off value (once a day) results in a much higher prevalence of the symptom cough in the whole population.

Handling causality and cut-off values explicitly are skills that require specific training for doctors involved in research. In daily practice doctors handle cut-off values intuitively and implicitly, they will not consider 'cough once a day' as an important symptom indicating a specific medicine. In a research setting this is more complicated, e.g., when is 'cough' part of the suspected COVID-19 illness. When doctors participate in research they will receive information about such subjects, but in every research project there are **misunderstandings**. Such misunderstandings should be detected by the investigators and this newsletter gives feedback in such cases.

### Aphorism 153 and Bayes' theorem

Every homeopathic practitioner knows that peculiar symptoms are more important than common symptoms. This is described in Hahnemann's aphorism 153, one of the most well known aphorisms of the Organon. This aphorism is directly related to (Bayesian) statistics: a symptom is peculiar when it has a low prevalence in the practice population, say, less than one in 200 patients (<0.5%). A common symptom has a much higher prevalence, say, more than 20%.

We can translate aphorism 153 directly into Bayes' theorem (posterior odds = LR x prior odds): peculiar symptoms are symptoms with high LR. Let us first look at a common symptom with prevalence of, say, 40%. Since a population responding well to a specific medicine is only a small part of the whole population, the denominator in the formula for LR (prevalence in the medicine population / prevalence in the remainder of the population) is close to the prevalence in the whole population. The theoretical maximum of LR of this common symptom is 100%/40%=2.5, supposing that every patient in the medicine population has the symptom.

Now, consider a peculiar symptom with a prevalence of 0.5%. In this case the theoretical maximum LR=100/0.5=200, supposing that every patient in the medicine population has the symptom - which is, of course, rarely the case.

Bayes' theorem places aphorism 153 in a more general context: higher LR indicates a better symptom and symptoms with low prevalence can have higher LRs than symptoms with high prevalence.

## Cut-off values

Symptoms can be peculiar because of the symptom itself, like 'Nausea hearing organ music', or by intensity. A 'desire for sweets' is quite common. If you ask 'Do you have a desire for sweets" and the patient responds "Yes", you will not directly start thinking about medicines like *Lycopodium*, but if the patient answers "YES!!" you will. If you already considered *Lycopodium* for this patient a 'normal' desire for sweets is a confirmation for this medicine. A strong intensity can make a symptom peculiar and this can result in high LR because the strong intensity has a lower prevalence.

Handling different cut-off values is done intuitively in daily practice. Each practitioner is also regarding the context of the patient. A salesman drinking coffee with all his customers will not directly be regarded as a 'desire for coffee', but a three year old child stealing the left-overs of coffee cups of visitors will.

In research there is a tendency to be precise. We would like to define 'desire sweets' and 'desire coffee' quantitatively, but we should not do that in homeopathic prognostic factor research! We need to use our expert judgement. This expert judgement intuitively compares the answer of the patient with our knowledge of the world, like in the example of 'desire for coffee' in a salesman or a young child.

Doctors recording symptoms of COVID-19 patients have to know the prevalence of these symptoms from available sources, such as the European Centre for Disease Prevention an Control (ECDC: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical ). We also apply our clinical judgement; a patient coughing a few times a day since years should not be recorded as having cough probably related to COVID-19.

## Detecting misunderstandings

As stated above, in all research projects there are misunderstandings between researchers and doctors recording data. The protocol and the instruction for observers is seldom complete and the instructions are more difficult to follow completely when they become more extensive. A common misunderstanding, however, is that doctors think 'the more, the better'. This leads to lowering cut-off values for symptoms and recording symptoms that would not be recorded in daily practice.

Recently, we came across a new batch of records where one doctor recorded four symptoms in all his twelve patients. When we compared this with the prevalence of these symptoms in the whole database we had at that moment and with the data of the ECDC we concluded that something must be wrong, see Table 1.

*Table 1: prevalence of four symptoms in 12 patients of one doctor, compared with the whole research population and ECDC data*

| | doctor A (%) | all (%) | ECDC |
|---|---|---|---|
| cough | 12/12 (100%) | 166/298 (55.7%) | 63.2% |
| fever | 12/12 (100%) | 131/298 (44%) | 45.4% |
| muscle pain | 12/12 (100%) | 123/298 (37.9%) | 62.5% |
| sore throat | 12/12 (100%) | 102/298 (34.2%) | 52.9% |

It is statistically highly unlikely that, even in a relatively small population, all COVID-19 patients have all four symptoms. The CDC numbers show that the prevalence of these four symptoms is close to 50%. Now, suppose that you flip a coin 4x12=48 times, how likely would 48 Heads be? However, there could be an underlying misunderstanding, possibly COVID-19 is only tested when a patient has these four symptoms.

Researchers should always be looking for 'outliers' in the data, like in this example. In such cases they have to contact the doctor involved to investigate if there is some misunderstanding of the research protocol. These misunderstandings can then be communicated with all participants in the research project. This prevents waste of effort for researchers and participating doctors. In this example all data coming from this doctor could not be included and previously accepted records (22 cases) had to be removed from the database with 298 records. Table 2 shows the differences in LRs for the four symptoms in Table 1.

*Table 2: LRs before (batch 1) and after (batch 2) removing 22 records with misinterpreted data collection*

| Symptoms | LRars1 | LRars2 | LRbry1 | LRbry2 | LRgels1 | LRgels2 |
|---|---|---|---|---|---|---|
| | n=298 | n=276 | n=298 | n=276 | n=298 | n=276 |
| cough | 0.66 | 0.70 | 1.12 | 1.24 | 0.83 | 0.89 |
| fever | 0.86 | 0.98 | 0.91 | 1.05 | 0.94 | 1.06 |
| muscle pain | 1.30 | 1.48 | 1.03 | 1.19 | 0.57 | 0.64 |
| sore throat | 1.24 | 1.45 | 0.85 | 0.99 | 0.79 | 0.90 |

Table 2 shows that removing 22 of 298 records (7.4%) resulted in higher LRs for these four symptoms, up to 16.9% higher. These 22 records were useless regarding the four symptoms because they did not indicate any difference between medicines. Therefore, deleting them resulted in higher LR values. The complete updated mini-repertory is shown in Table 3 in the Appendix.

## Discussion

Misunderstandings of protocols and instructions are unavoidable in any research project. It is a joined responsibility of researchers and observers to avoid such misunderstandings and researchers must detect them as soon as possible and give feedback to the observers. We apologise for detecting this problem a bit late. It is not always possible to detect such problems when inspecting the data. Statistical analysis might help, but is not always feasible. This project is a compromise between assessing homeopathic symptoms in a new disease as soon as possible to inform homeopathic practitioners on the one hand and avoiding bias by longer preparation on the other hand.

## Conclusion

Misunderstanding of protocols and instructions is unavoidable in clinical research. Monitoring of data and feedback to doctors collecting the data is essential for improving the quality of the data.

## Resuming requisites for case descriptions

We resume the minimal necessary data for this project. We already had:

- Severity of COVID-19 illness: Mild – Moderate – Severe – critical
- Is COVID-19 confirmed?
- Medicine, with date of first intake
- Number of hours until onset of improvement and/or until absence of fever
- If possible at least 3-5 symptoms that were characteristic for the case
- Pneumonia on X-ray or CAT

Also check:

- Number of days between first symptoms and deteriorated condition
- Prostration/exhaustion; where is the weakness seated
- Fear/anxiety
- Confusion
- Restlessness
- Fever, chill, or chill alternating with fever
- Thirst
- Pain; where
- Cough dry or moist
- Dyspnea
- Throat pain
- Loss of taste and/or smell
- diarrhoea

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## Appendix

*Table 3: mini-repertory of COVID symptoms based on 276 records (20 July 2020), after removing questionable records*

| Symptoms | Count | LRars | LRbry | LRgels |
|---|---|---|---|---|
| n= | 276 | | | |
| fatigue | 154 | 1.26 | 0.75 | 1.68 |
| cough | 144 | 0.70 | 1.24 | 0.89 |
| dry cough | 122 | 0.80 | 1.38 | 0.93 |
| fever | 109 | 0.98 | 1.05 | 1.06 |
| muscle/bone pain | 103 | 1.48 | 1.19 | 0.64 |
| headache | 99 | 0.70 | 1.44 | 1.48 |
| throat pain | 84 | 1.45 | 0.99 | 0.90 |
| dyspnea | 76 | 0.40 | 1.00 | 0.78 |
| chill | 73 | 0.65 | 0.93 | 3.07 |
| chest discomfort | 68 | 0.62 | 0.95 | 0.89 |
| anxiety/fear | 65 | 3.51 | 0.42 | 0.32 |
| dry mouth/throat | 53 | 0.48 | 0.86 | 0.13 |
| loss of taste and/or smell | 53 | 1.66 | 0.77 | 1.01 |
| diarrhoea | 52 | 2.06 | 1.93 | 0.41 |
| thirst | 50 | 2.39 | 2.07 | 0.28 |
| thirstless | 29 | 0.17 | 0.69 | 3.51 |
| chest pain | 29 | 0.53 | 1.61 | 0.77 |
| heat body | 27 | 2.73 | 0.92 | 0.26 |
| loss of appetite | 23 | 3.56 | | 1.00 |
| nausea | 21 | 1.09 | 0.44 | 0.33 |
| back pain | 20 | 2.49 | 0.88 | 1.18 |
| chest pain < cough | 19 | 0.26 | 3.62 | |
| productive cough | 18 | 0.27 | 3.29 | 2.56 |
| taste altered | 17 | 1.43 | 2.34 | 0.42 |
| heaviness eyelids | 15 | | 0.96 | 10.00 |
| cough < talking | 14 | 0.00 | 0.44 | 86.67 |
| > open air | 14 | 0.77 | 1.97 | |
| chill back | 14 | 0.77 | 1.05 | 1.11 |
| perspiration | 13 | 0.39 | 1.64 | 0.56 |
| desire cold drinks | 13 | | 1.64 | 0.56 |
| thirst large quantities | 12 | | 28.95 | |
| taste bitter | 11 | 1.74 | 0.58 | 0.67 |
| > lying | 11 | 1.74 | 1.50 | 0.67 |
| cough < deep respiration | 11 | 0.46 | 4.61 | 0.67 |
| desire warm drinks | 11 | 1.03 | 7.02 | |
| sleeplessness | 10 | 10.81 | 0.66 | |
| restless | 10 | 1.99 | 0.66 | 0.74 |