Setting new horizons for data collection: the Clificol COVID-19 Support Project

The Clificol Team – 30th Sep 2020

Abstract

The Clificol® COVID-19 Support Project is an innovative international data collection project, carefully designed by a group of experts in homeopathy and research, aimed to tackle some of the core questions in homeopathy.

The project aims firstly to describe of the demographics, geographics specificities and time-courses of the epidemic and offer some light on the notion of *Genus Epidemicus* in this infection (through common remedies and rubrics). Going beyond that, the project aims to use this unique data to tackle more fundamental questions in homeopathy such as the notion of individualization and the law of similars. In this sense the Clificol-COVID19 project offers a unique way to make use of the current crisis to strengthen the foundations of homeopathy philosophy and practice.

In this publication the preliminary analysis is presented **to demonstrate the potential of our approach**, and how powerful it can be if we collect enough data. The more cases are entered, the better we will be able to explore these issues, making best use of this tragic and unprecedented pandemic. So, we need as many homeopaths to contribute their cases as possible.

Background and Rationale of the Clificol Project

As many of you already know, in the past year we placed a lot of effort in the creation of a **new and free** online platform to collect homeopathic data worldwide. While the Clificol project started many years ago, we put together an amazing team of scientists, homeopaths and homeopathic associations to collaborate on a COVID-19 Support data collection Project. With the support of many active homeopaths around the world, we have well over 450 COVID-19 cases in the database by now!

Besides the research design and statistical considerations, the team also paid extra effort to ensure all potential contributors are properly vetted, to make sure the whole platform is compatible with GDPR/HIPAA and privacy regulations, and to safeguard the project and contributors from any legal and ethical concerns. With the active participation of more homeopaths, the multilingual interface will provide valuable data not only for the Clificol project, but also other research groups in our field.

The Clificol project does not aim to reach any conclusion about the efficacy of homeopathic treatment of COVID-19. To reach any firm conclusion regarding efficacy, would require a comparable non-homeopathy group (for placebo/confounder control). The Clificol project being composed of a single group (all cases being treated with homeopathy), it is impossible make any inference with respect to efficacy, i.e. causality of homeopathic treatment in positive clinical outcome. As the condition is mostly self-limiting, making any inference about effectiveness of homeopathy for the treatment of COVID-19 in usual clinical practice is also inherently fraught with difficulty and as such this is not the aim of this study.

On the other hand, there are other ways to use this data. In particular, if we go beyond the idea that only some form of trial would be able to strengthen the case of homeopathy we see, using *Hill's Criteria for Causation* (one of the most commonly referred guide for causality judgement), that experimental evidence (such as cohort studies, randomized control trials RCT and so on) is just one of nine domains to be taken into consideration. These domains are:

- Experimental evidence (e.g. randomized control RCTs)
- Strength of association
- Temporality
- Specificity
- Analogy
- Biological gradient (Dose-response relationship)
- Consistency (Repeatability)
- Plausibility (Physio-chemical studies)
- Coherence (*Predictive performance, Susser 1991)

If we are to study the possible causality relationship between homeopathic treatment and evolution of diseases, then we should not only consider RCTs to stand in defense of homeopathy. The current debate around homeopathy makes the need for a wider approach, beyond 'just RCTs' ever clearer. Many other types of studies could help people better understand the phenomena experienced by homeopaths over the past 200 years.

Therefore, one of the main aims of the Clificol project is to study the so-called 'predictive performance' in the practice of homeopathy, i.e. when a patient presents the symptom picture of a given remedy does the prescription of this remedy correlate with a relative faster recovery. The vast amount of similar cases occurring over the same period worldwide provides a unique opportunity for this kind of study.

Why is predictive performance important?

A measure of the predictability of the effect of homeopathic prescriptions can give evidence to support the idea that homeopathic prescriptions and the subsequent case evolution are not a random phenomenon imagined by homeopaths, i.e. that successful homeopathic prescriptions are not random but follow certain rules which make the clinical outcome predictable.

In this article, we will introduce some of the methods used in the Clificol project to assess the predictive performance of homeopathic prescriptions and the subsequent case evolution. The following two approaches aim at providing more solid support for the most important principles in homeopathic practice.

a. How closely does the presentation of a particular symptom picture (identified by statistical analysis) associate with case success when corresponding remedy is prescribed?

   Validation of the notion of ***Individualisation****, i.e. Patients tend to present distinct, well defined symptom pictures which correspond to the indicated remedy*

b. Can the association between symptom picture and successful remedy prescription be modelled using mathematical prediction models?
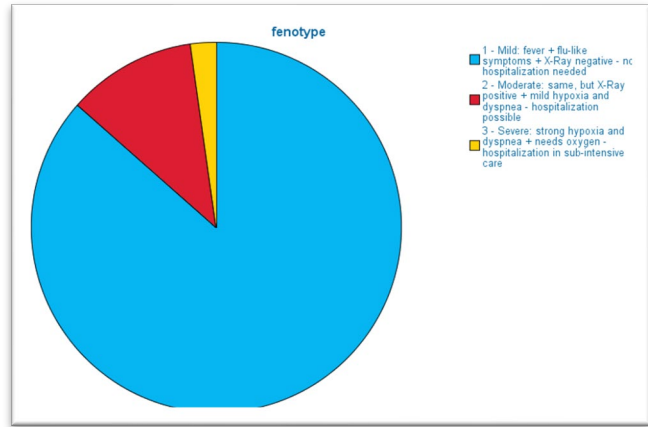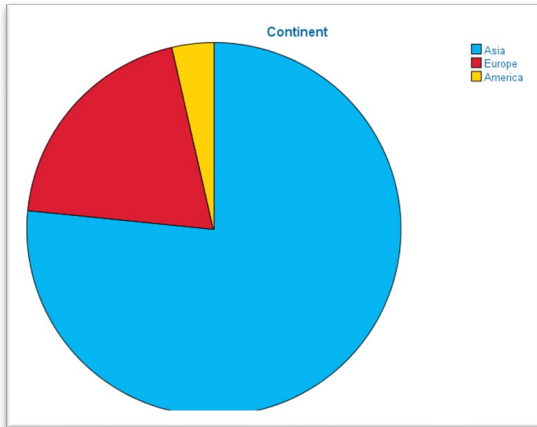
   Validation of the ***Law of Similars****, i.e. the homeopaths skill of finding the remedy most similar to a patient's symptom picture*

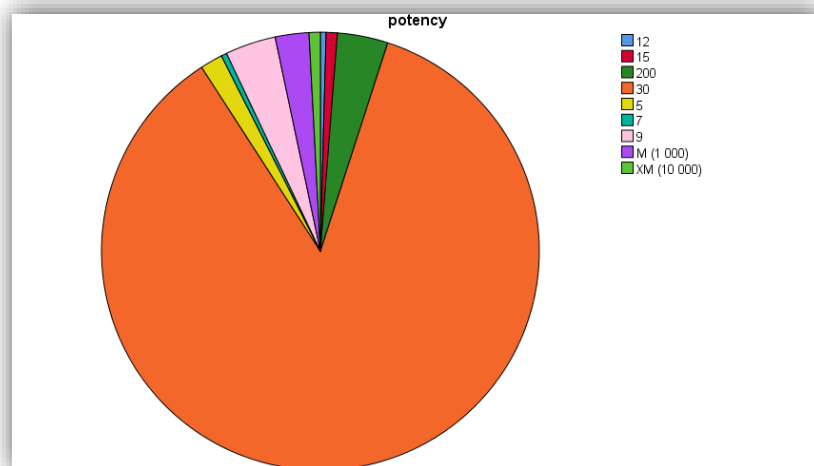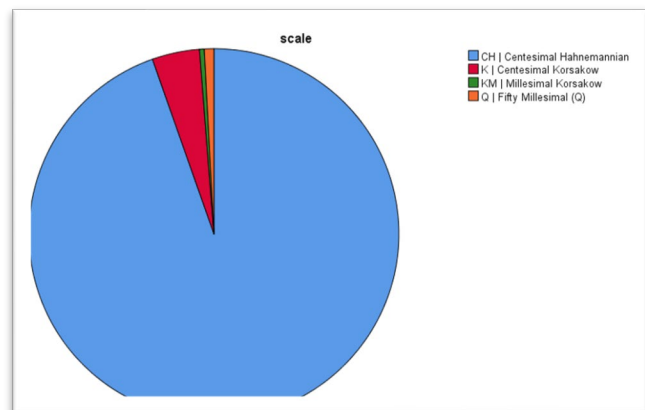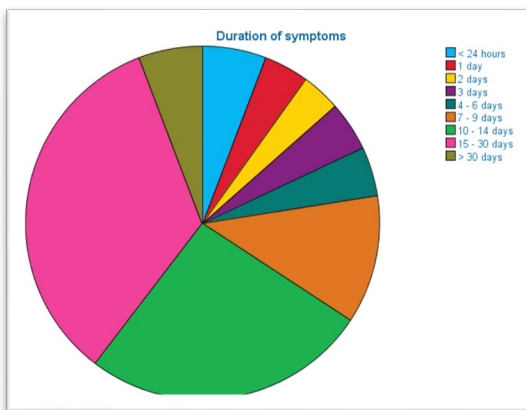# Preliminary results of the analysis using limited data

The data for this preliminary analysis phase was extracted from the Clificol COVID 19 database, corresponding to cases entered in May and June, up to the 1st of July 2020. The dataset consisted of 261 cases, 222 of which had enough data for analysis. The number of prescriptions available for analysis from these cases was 241. 71.6% of the cases were still in progress. Basic demographic data were as shown in the figures: 57.7% were female, with a mean age of 41.5 ± 13.9-year-old (Minimum: 0-year-old; Maximum: 89-year-old). The largest age group was 30-44-year-old (43.7%).
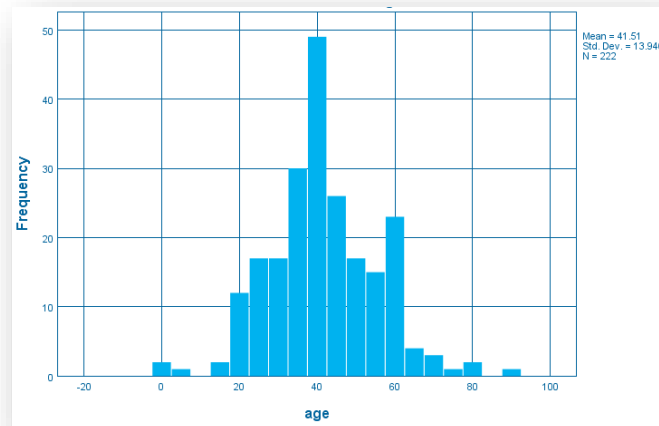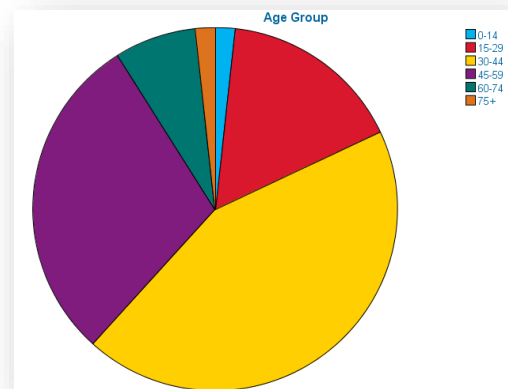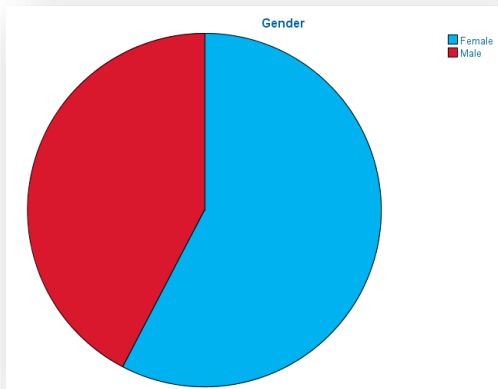

The majority of the cases were from Asia where the pandemic first started, followed by Europe and America. There were no cases from other continents at that time. 86.5% of the cases were categorized as 'mild' when they started homeopathy, none of them were considered 'critical' or 'very critical' at the first consultation.

Continent
- Asia
- Europe
- America

fenotype
1 - Mild: fever + flu-like symptoms + X-Ray negative - no hospitalization needed
2 - Moderate: same, but X-Ray positive + mild hypoxia and dyspnea - hospitalization possible
3 - Severe: strong hypoxia and dyspnea + needs oxygen - hospitalization in sub-intensive care

Most cases presented themselves to a homeopath 7 to 9 days, 10 to 14 days or 15 to 30 days after symptom onset (11.7%, 26.1% and 33.8% respectively). 85.7% of the first prescription used a 30C potency, while 94.1% of them used the CH potency range.

Duration of symptoms
- < 24 hours
- 1 day
- 2 days
- 3 days
- 4 - 6 days
- 7 - 9 days
- 10 - 14 days
- 15 - 30 days
- > 30 days

scale
- CH | Centesimal Hahnemannian
- K | Centesimal Korsakow
- KM | Millesimal Korsakow
- Q | Fifty Millesimal (Q)

potency
- 12
- 15
- 200
- 30
- 5
- 7
- 9
- M (1 000)
- XM (10 000)

In this set of data, Gelsemium sempervirens (57.7%), Bryonia alba (19.9%) and Arsenicum (4.1%) were the three most common remedies in use.

Top remedies with frequency >1
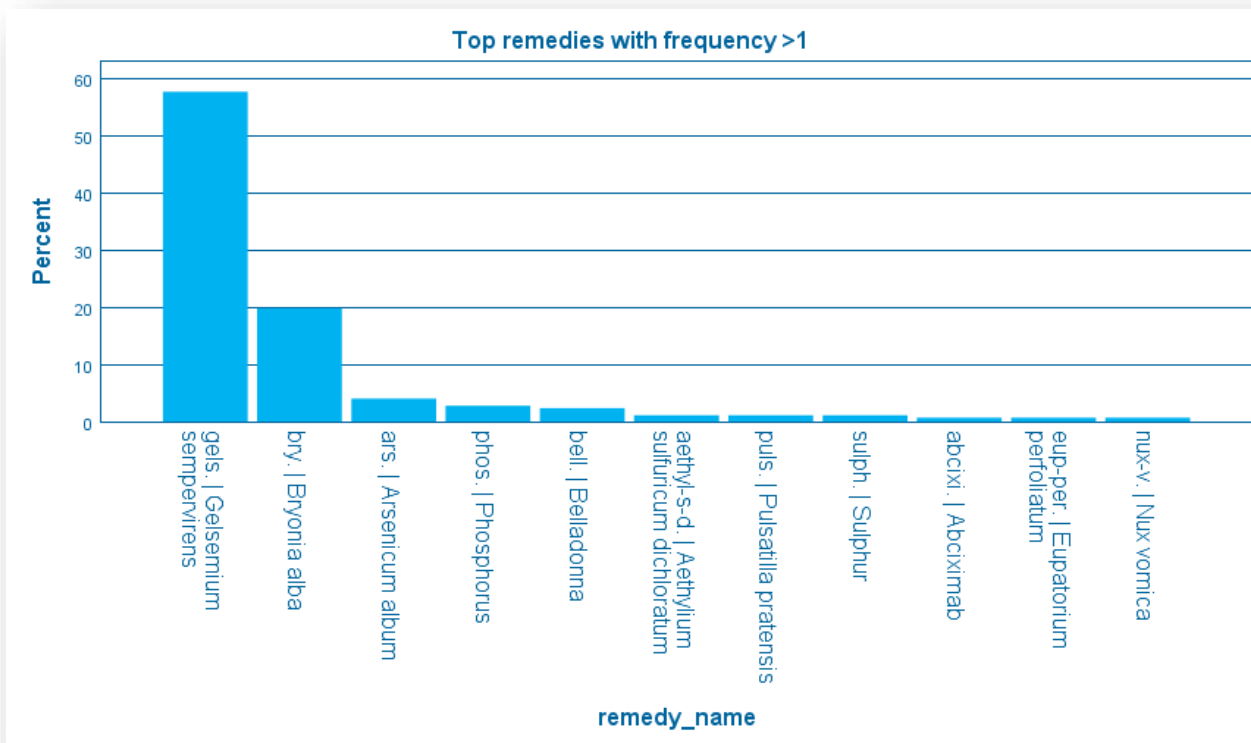
The top rubrics for successful Gelsemium sempervirens prescriptions (as defined by the faster recovery cases within the homeopathy treated cases) include:

MIND – DULLNESS
SLEEP – SLEEPINESS
GENERALS - WEAKNESS
GENERALS - SLOW MANIFESTATION
GENERALS - WEATHER - wet weather - agg.
GENERALS - PERSPIRATION - after - amel.
CHILL - BEGINNING IN - Back
FEVER - ALTERNATING WITH - chills
STOMACH - THIRSTLESS
HEAD - CONSTRICTION - band or hoop
HEAD - PAIN - urination - profuse - amel.
EYE - HEAVINESS - Lids
COUGH - EXHAUSTING
COUGH – TICKLING
EXPECTORATION - INFREQUENT
BLADDER - URINATION - involuntary - cough agg.; during
BACK - PAIN - Cervical region - Nape of neck - extending to - Head

The top rubrics for successful Bryonia alba prescriptions include:

> MIND - COMPANY - aversion to
> MIND - IRRITABILITY
> SLEEP - SLEEPINESS
> GENERALS - PERSPIRATION - after - amel.
> GENERALS - WEATHER - wet weather - agg.
> GENERALS - MOTION - agg.
> STOMACH - THIRST - large quantities; for
> STOMACH - THIRST
> HEAD - PAIN - motion - eyes; of - agg.
> HEAD - PAIN - Forehead - Eyes – Above
> HEAD - HANDS - holds head with - cough agg.; during
> HEAD - COUGH - during - agg.
> CHEST - PAIN - holds chest with hands during cough
> CHEST - PAIN - cough - during - agg.
> COUGH - CONSOLATION AGG.
> COUGH - ANGER; AFTER
> COUGH – EXHAUSTING
> BLADDER - URINATION - involuntary - cough agg.; during

Validation of the notion of Individualization (Cluster analysis)

As explained before, assessment of the predictive performance of homeopathic prescriptions and the subsequent case evolution may help provide more solid support for the most important principles in homeopathic practice.

The principle of 'Individualized treatment' in homeopathic prescription can be approached with cluster analysis. The research question is: *Is there any difference in symptomatic presentation among COVID-19 cases?*

Cluster analysis looks for groups with common features within a larger set of people based on information about the people (e.g. customers for marketing purposes). In the Clificol Project, we investigated the 241 consultations from the preliminary dataset, each consultation has a number of associated rubrics. In this preliminary analysis, we concentrated on the 50 overall most common rubrics. The clusters are constructed looking for similarities between the sets of rubrics found in each consultation.

Preliminary analysis:

SPSS®26 clustering algorithm found 3 clusters in the data. Cluster 1 (N=119) is the largest while Cluster 3 (N=26) is the smallest. The Cluster separation is shown as below:
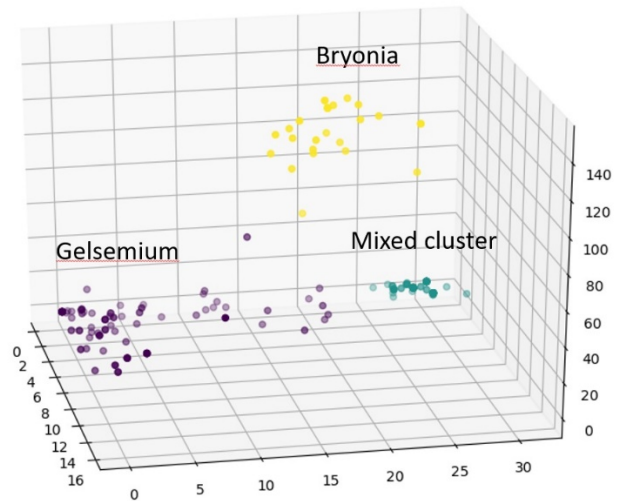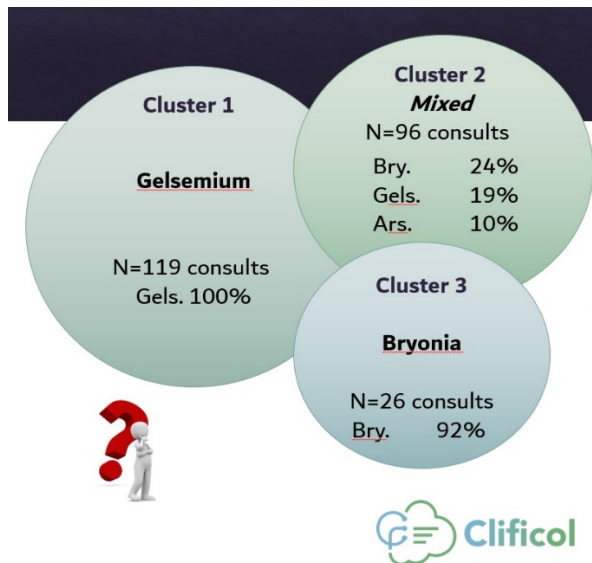
The preliminary analysis picks up the two most common remedies pictures corresponding to Gelsemium sempervirens (Cluster 1) and Bryonia alba (Cluster 3). Interestingly it finds another remedy picture (Cluster 2, N=96), which is more of a mixture between Gelsemium sempervirens and Bryonia alba.

The success rate of the cluster 1, 2 and 3 were 99%, 75% and 100% respectively, showing a much lower success rate in cluster 2. We can therefore suspect that this remedy picture is quite distinct from the either Bryonia alba or Gelsemium sempervirens cluster, and it could be very interesting to study this distinct set of cases which emerges from the statistical analysis. With a larger sample size, it is very likely that more clusters would be identified, isolating out different symptom pictures (e.g. those purple spots in between clusters).

The cluster analysis can provide more mathematical evidence to support the notion that *there are different kind of COVID-19 patients, and individualization in homeopathic practice according to symptom pictures therefore makes sense even when the underlying cause is in principle identical.*

Validation of the Law of Similars (Regression modelling)

Assessment of the predictive performance of homeopathic prescriptions and the subsequent case evolution may also help providing more solid support for another important principles in homeopathic practice ---- 'Law of Similars'.

This principle can be investigated using regression modelling. The question is: *Do homeopathic symptom patterns correlate with successful homeopathic prescriptions of a corresponding remedy in COVID-19 patients?*

Three distinct clusters were identified using cluster analysis, in regression modelling, we initially focused on the cluster 1 (Gelsemium sempervirens) to demonstrate the strength of the approach.

For this analysis we defined a case as a 'Success' if it showed relatively faster recovery i.e. improvement in day 1 and day 3 outcome assessments and no relapse at day 7. 'Failure' was defined as not meeting the above criteria, or the 'success' of other remedies.

Demonstration of Regression model (Gelsemium sempervirens)

In the demographic table, it is found that the successful Gelsemium sempervirens cases were significantly younger, with milder symptoms, and longer symptom onset.

	Gelsemium success N=136 (%)	Gelsemium failure N=83 (%)	P-value
Gender			
Female	73 (53.7%)	58 (69.9%)	0.18
Male	63 (46.3%)	25 (30.1%)	
Age			
Mean (SD)	39.75 ± 10.6	45.5 ± 16.9	<0.01[a]
0-14	0 (0%)	2 (2.4%)	<0.01
15-29	22 (16.2%)	14 (16.9%)	
30-44	74 (54.4%)	21 (25.3%)	
45-59	35 (25.7%)	34 (41%)	
60-74	4 (2.9%)	9 (10.8%)	
75+	1 (0.7%)	3 (3.6%)	
Severity			
Mild	134 (98.5%)	59 (71.1%)	<0.01
Moderate	1 (0.7%)	22 (26.5%)	
Severe	1 (0.7%)	2 (2.4%)	
Critical	0 (0%)	0 (0%)	
Duration of symptoms			
Median (IQR)	22.5 (12.0 – 22.5)	12.0 (0.5 – 22.5)	<0.001[b]

[a] Independent T-test
[b] Mann-Whitney U test

Clificol

In the crude odd ratio analysis, nearly all top rubrics were significantly related to the success of the remedy. However, adjusted odd ratio of many of the top rubrics were different from the crude odd ratio by more than 10%, thus confounding effect were present when we considered the set of symptom pattern as a whole, but not individual symptom. Some of the examples are shown below:

	Crude OR (95%CI)	Wald test P-value	Omnibus test (=LRT) P-value	Adjusted OR (95%CI)	Wald test P-value
Age	0.97 (0.95 – 0.99)	0.003	0.002	0.97 (0.92 – 1.02)	0.27
Severity	0.066 (0.02 – 0.2)	<0.001	<0.001	2.15 (0.33 – 14.2)	0.43
Duration of symptoms	1.073 (1.0 – 1.1)	<0.001	<0.001	0.96 (089 – 1.04)	0.36
EYE - HEAVINESS - Lids	158.2 (55.2-452.9)	<0.001	<0.001	6.3 (0.32 – 124.6)	0.23
CHILL - BEGINNING IN - Back	158.2 (55.2-452.9)	<0.001	<0.001	4.3 (0.14 – 133.0)	0.41
STOMACH - THIRSTLESS	109.0 (41.1 – 289.4)	<0.001	<0.001	6.8 (0.61 – 76.4)	0.12
HEAD - CONSTRICTION - band or hoop	27.9 (12.8 – 60.8)	<0.001	<0.001	0.11 (0.01 – 2.70)	0.18
MIND - DULLNESS	17.1 (8.6 – 34.0)	<0.001	<0.001	18.8 (1.8 – 194.4)	0.01
COUGH - NIGHT	3.8 (0.5 – 32.0)	0.22	0.16	14.8 (0.4 – 539.6)	0.14
BLADDER - URINATION - involuntary - cough agg.; during	26.1 (11.9 – 57.6)	<0.001	<0.001	0.23 (0.01 – 4.2)	0.32
HEAD - PAIN - urination - profuse - amel.	510.3 (109.0 – 2389.0)	<0.001	<0.001	193.4 (7.5-5020.4)	<0.01

To adjust for the confounding effect among the rubrics and baseline features, and select the most significant rubrics for the remedy, logistic modelling selection can be performed with drop-in-deviance test (likelihood test). The preliminary result on the beta-testing data was as follows:

	Beta	Adjusted OR (95%CI)	P-value
Age	-0.034	0.97 (0.92 – 1.02)	0.22
MIND - DULLNESS	1.628	5.10 (0.94 – 27.61)	0.06
EYE - HEAVINESS - Lids	1.644	5.17 (0.75 – 35.80)	0.10
STOMACH - THIRSTLESS	1.799	6.05 (0.79 – 46.21)	0.08
COUGH - NIGHT	2.438	11.46 (0.52 – 250.9)	0.12
HEAD - PAIN - urination - profuse - amel.	3.704	40.62 (4.30 – 383.35)	0.001

What does it mean?

Using this mathematical model, we are able to calculate the expected probability that a patient will benefit from taking Gelsemium sempervirens.

For example, a COVID-19 patient aged 30, presenting with dullness, heaviness of eyelids, thirst, cough aggravated at night, and no headache ameliorated from profuse urination, would have a probability of success of a Gelsemium sempervirens prescription of 88%.

We can calculate the **sensitivity** and **specificity** of the model: with a cutoff of 0.79, the sensitivity is 0.96 and specificity is 0.98. Thus, from the preliminary model,

- When the patient is a Gelsemium sempervirens case, there is 96% of chance that it can be found out.
- When the patient is a not Gelsemium sempervirens case, there is 98% of chance that it can be found out.

The same procedure can be done on the other clusters, the preliminary model generated for the Bryonia alba cluster has a sensitivity of 0.89 and specificity of 0.91. In the future when the sample size increases, it can be done on all clusters identified, the next models expected from the current data are likely to be for Phosphorus and Arsenicum album.

With more data we will be able to explore more complex models and figure out whether there is any statistical evidence for other common homeopathic concepts such as Keynote symptoms and the "three-legged stool".

Conclusion:

Collecting data about patient prescriptions and clinical outcomes during the COVID pandemic will allow us to test some of the core principles of homeopathy from a rigorous scientific perspective in a unique way, using state of the art statistical techniques. The Clificol COVID-19 data collection project, current supported by most of the organizations worldwide, requires more cases in order to fulfills its ambitious aims – if you are a homeopath and you have COVID cases please consider contributing your cases.

Acknowledgement:

With the support of ECH, ECCH, ICH, HRI, LMHI, and other professional associations, the Governance Committee now consists of 11 representatives, representing 197 associations. More than 35 national coordinators are now working together for the qualification verification. Special thanks are given to the Scientific Committee for their expert advice, and Zeus-soft® for their generosity to make the software, extra programming effort and technical support universally available for free!

The project aims at collecting >2020 cases before the end of this unforgettable year of 2020, the project cannot be successful without the **ACTIVE PARTICIPATION** of international colleagues like **YOU**. To learn more about the project, please visit: https://clificol.net/en/Information-pack .

References:

1. Hill, Austin Bradford. "The environment and disease: association or causation?" (1965): 295-300.
2. Susser, Mervyn. "What is a cause and how do we know one? A grammar for pragmatic epidemiology." American Journal of Epidemiology 133.7 (1991): 635-648.