Data Collection during the COVID-19 Pandemic: Learning from Experience, Resulting in a Bayesian Repertory

Lex Rutten[1] Tom Smedley[2] Galen Ives[3] Peter Gold[4] Bernardo Merizalde[5] Robbert van Haselen[6] Raj Kumar Manchanda[7] Ashley Ross[8] Gustavo Cataldi[9] Altunay Agaoglu[10] Tiziana di Giampietro[11] Theodore Lilas[12] Frederik Schroyens[13] José E. Eizayaga[14]

[1] Independent Researcher, Breda, the Netherlands
[2] Independent Researcher, United Kingdom
[3] Information School, University of Sheffield, United Kingdom
[4] American Institute of Homeopathy (AIH), United States
[5] Department of Integrative Medicine and Scientific Nutrition, Thomas Jefferson University, Philadelphia; Liga Medicorum Homeopathica Internationalis (LMHI), United States
[6] International Institute for Integrated Medicine, Kingston, United Kingdom
[7] Directorate of AYUSH, Govt. of Delhi, India
[8] Durban University of Technology, Durban, South Africa
[9] Liga Medicorum Homeopathica Internationalis (LMHI), Argentina
[10] Liga Medicorum Homeopathica Internationalis (LMHI), Turkey
[11] European Committee for Homeopathy (ECH), Italy
[12] Vithoulkas Compass, Greece
[13] ZEUS-SOFT, Belgium
[14] Department of Homeopathy, Maimonides University, Argentina

Address for correspondence Lex Rutten, MD, Independent Researcher, Aard 10, 4813 NN Breda, The Netherlands (e-mail: praktijk@dokterrutten.nl).

Homeopathy 2021;110:94–101.

Abstract

Background A novel pandemic disease offered the opportunity to create new, disease-specific, symptom rubrics for the homeopathic repertory.

Objective The aim of this study was to discover the relationship between specific symptoms and specific medicines, especially of symptoms occurring frequently in this disease.

Materials and Methods Worldwide collection of data in all possible formats by various parties was coordinated by the Liga Medicorum Homeopathica Internationalis. As the data came in, more symptoms were assessed prospectively. Frequent analysis and feedback by electronic newsletters were used to improve the quality of the data. Likelihood ratios (LRs) of symptoms were calculated. An algorithm for combining symptom LRs was programmed and published in the form of an app. The app was tested against 18 well-described successful cases from Hong Kong.

Results LRs of common symptoms such as 'Fatigue' and 'Headache' provided better differentiation between medicines than did existing repertory entries, which are based only on the narrow presence or absence of symptoms. A mini-repertory for COVID-19 symptoms was published and supported by a web-based algorithm. With a choice of 20 common symptoms, this algorithm produced the same outcome as a full homeopathic analysis based upon a larger number of symptoms, including some that are traditionally considered more specific to particular medicines.

Conclusion A repertory based on clinical data and LRs can differentiate between homeopathic medicines using a limited number of frequently occurring epidemic symptoms. A Bayesian computer algorithm to combine symptoms can complement a full homeopathic analysis of cases.

Keywords
- COVID-19
- repertory
- Bayes' theorem
- data collection
- prognostic factor

received
August 11, 2020
accepted after revision
September 9, 2020
published online
December 21, 2020

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0040-1718583.
ISSN 1475-4916.

Introduction

Since the end of 2019, the whole world has become affected by an epidemic of the coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus. By the end of May 2020, more than six million confirmed cases had been reported and about 370,000 deaths.[1] At that time, no vaccination was available and no effective therapy had been reported.

COVID-19 patients display a wide range of symptoms, but the most frequent are: fever or chills; cough; shortness of breath or difficulty breathing; fatigue; muscle or body aches; headache; recent loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting and diarrhoea.[2] This range of symptoms makes it difficult to gain a clear perspective on how homeopathy can be applied in this epidemic. Former epidemics have shown that a limited number of homeopathic medicines can be used in the treatment of the disease because the symptoms produced by the microorganism predominate over constitutional symptoms. However, with the range of symptoms caused by the infection in different patients we may expect a variety of eligible homeopathic medicines, because the totality of those symptoms does not clearly indicate one single homeopathic medicine.

An initial selection of homeopathic medicines could be based on the symptomatology of the epidemic by repertorisation (the repertory is an index to the symptoms of all medicines in the homeopathic materia medica). This, however, results in a large number of possible medicines because symptoms such as 'fever', 'weakness', 'dry cough', 'loss of smell' and 'dyspnoea' are very common, and this results in large repertory rubrics. Alternatively, the choice of possible medicines could be based on previous epidemics.[3] Other possible criteria could derive from fundamental research, such as the finding that *Bryonia alba* contains flavonoids which have an inhibitory effect on peroxidase-catalysed oxidation,[4] relating this to the possible role of the angiotensin-converting enzyme 2 receptor and protease inhibitors in this disease.[5]

The most important question, however, is this: What works in daily practice? All over the world, patients have been treated with homeopathy, and case descriptions can be a valuable source of information, particularly if they show us which medicines have been used successfully and which symptoms indicate specific medicines. In this article, we report how a working group of the Liga Medicorum Homeopathica Internationalis (LMHI) collected and analysed cases of COVID-19-like illness. This was not only a process of learning from homeopathic experience but also of learning how to collect data and evaluate a new disease. There was no completely worked-out protocol at the outset; this was adapted as data came in. The protocol was, therefore, also partly a product of learning from experience. We applied modern statistical techniques to assess the data, which were translated into a Bayesian mini-repertory, presented in an app containing a Bayesian algorithm for combining symptoms to differentiate between medicines.

Methods

The primary objective of our evaluation was to discover the relationship between specific symptoms and specific medicines, especially of symptoms occurring frequently in this disease. Such relationships enable a more precise differentiation between medicines by applying Bayes' theorem.

We collected, and are still collecting, data from cases with confirmed COVID-19 (by PCR, etc.) and where COVID-19 is suspected because of a combination of symptomatology and COVID-19 contact. Clinicians were invited to submit data in any available format (such as text, spreadsheet or database) through every network we could find. Such networks were: LMHI, European Council for Homeopathy (ECH), American Institute of Homeopathy (AIH), Ärztegesellshaft für Klassische Homöopathie (ÄKH), as well as published[6] and unpublished case series. Most cases were submitted by the AIH, which use a web-based questionnaire with pre-formatted questions such as 'dry or productive cough', 'fever', as well as free text fields for full case descriptions. Such symptoms were standardised for quantitative analysis.

We first undertook a qualitative analysis of each case: Was the illness and reaction to therapy well described? Were homeopathic symptoms well described? Were other (homeopathic) therapies prescribed that could have influenced outcome? If it appeared likely that a specific homeopathic medicine was related to the improvement of the patient, the case was entered into an Excel spreadsheet. The qualitative analysis was done by author LR; in unclear cases consensus was sought with author PG. The spreadsheet and discussion points were shared with all authors after standardisation of symptoms. Contributors of cases were instructed to anonymise cases and follow ethical guidelines of their countries. Anonymity was also guaranteed by the standardisation of symptoms. In some countries, such as India, ethical clearance was obtained. Generally, ethical clearance and informed consent were waived because the data analysis was based on registration of normal daily practice. The use of anonymised data is in agreement with the European Data Protection Law (EU) (2016/679, article 89).[7] The spreadsheet contained some pre-defined variables to categorise each anonymised case (patient code, gender, age, country, practitioner), the prescribed medicine, the severity of the case, laboratory confirmation, prescribed medicine, time to onset of improvement and presence or absence of fever and result of the medicine. Symptoms not corresponding to any of those pre-formatted were initially entered in cells as free text.

Many of the unformatted symptoms were complex. A symptom such as 'Headache, worse during the night' had to be split into the symptom 'Headache' and the sub-symptom 'Headache, worse during the night', to allow all cases with headache to be counted separately. The next step was to standardise symptoms with synonymous descriptors: for example, of the symptom 'fatigue'. The 'fatigue' in COVID-19 cases is more than straightforward tiredness, and several different expressions such as 'prostration', 'heaviness' and 'weakness' were used by different practitioners. We chose the word

'fatigue' because it was the most frequently used, for example, by the World Health Organization.

The project began in March 2020, at which time there were few data and the contributors generally had no experience of data collection. A newsletter was sent frequently to the contributors, giving instructions, showing results and providing feedback. The basic principles of a Bayesian repertory, applying likelihood ratio (LR), were explained step-by-step using data from the case collection. The collected data were also used to demonstrate sources of bias. A growing list of symptoms that appeared in many cases was added to the pre-defined variables of the spreadsheet and contributors were asked to check these symptoms in every patient. The outcome of qualitative and quantitative analysis of the spreadsheet was disseminated among LMHI members.

Cases were collected and analysed on a weekly basis and new synonyms were merged. These data sufficed to calculate the constituents of the LR; $LR = (a/(a + c))/(b/(b + d))$:

a = The number of patients in the population responding well to the medicine with the symptom.
b = The number of patients in the remainder of the population with the symptom.
c = The number of patients in the population responding well to the medicine without the symptom.
d = The number of patients in the remainder of the population without the symptom.

The 95% confidence interval (CI) of some LRs was calculated with Confidence Interval Analyser (BMJ).

To facilitate the necessary calculations for a combination of symptoms, an app was developed, calculating the combined LRs. The app was built using Webflow, which allows the programmer to build the app visually using its editor. The part of the app that combines LRs to recommend medicines uses JavaScript, as this allows the calculations to take place immediately on the user's device rather than the distant server. This also allows us to use Netlify, a cloud computing company which distributes the website globally, providing the fastest response wherever the user is in the world. Additionally, hosting on Netlify is free of charge. The combination of Webflow + JavaScript + Netlify allowed us to produce the website quickly and ensure that it operates with the greatest global speed. The app was also designed to be easy to update with further symptoms, medicines and data.

The app was tested with a published case series of 18 cases.[6] Out of these 18 cases, 17 had been prescribed medicines that were included in the database underlying the app, whilst one had received another medicine. The question was: Does the use of only the most frequently occurring symptoms in an initial screening give results that are consistent with the outcome of the standard homeopathic method using all available symptoms, common and particular? We also calculated a correlation matrix between each of the symptoms of the app using Pearson's contingency coefficient.

Patients

By the end of May 2020, 161 patients (91 females, 58 males and 12 unknown gender) were included from Argentina, Austria, Belgium, Brazil, China, France, Germany, India, Iran, Italy, the Netherlands, Turkey and the United States. Age range: 0 to 84 years.

Results

By the end of May, 161 cases had been collected, for whom 31 homeopathic medicines were prescribed. The most prescribed medicines were *Bryonia alba (Bry)* ($n = 45$), *Gelsemium sempervirens* (*Gels*) ($n = 25$), *Arsenicum album* (*Ars*) ($n = 21$), *Phosphorus (Phos)* ($n = 12$) and *Camphora (Camph)* ($n = 12$). *Bry*, *Gels* and *Ars* represented 91 cases (56.5% of the total), *Phos* and *Camph* another 14.9%. Six medicines had 3 to 6 cases, four medicines had two cases and 16 medicines one single case each. The total number of symptoms recorded was 1404.

Symptoms from various sources were first entered in free text cells, as shown in ►**Fig. 1**. If necessary, symptoms with modalities were split into symptom and sub-symptom.

Symptom 1	Symptom 2	Symptom 3	Symptom 4
Fever alternating with chill	Restlessness especially at night	Fear of dying	Increase in thirst, with desire for very hot drinks
No obvious fever but prominent chilliness	Thirstiness but could only take small sips of water	Drinking aggravated nausea and diarrhoea	Nausea aggravated from the smell of food
Slow onset/progression	Fever was alternating with chilliness	Generally aggravated from cold and wet weather	Generally ameliorated from warm and dry air
Slow onset/progression	Fever was alternating with chilliness	Cough aggravated by all motion, talking, lying down, and waking in the morning	Motion aggravates chest pain
Intense need to lie down without the energy to get up	Soreness all over	Cold perspiration	Dry coughs

Fig. 1 Part of the actual database. Symptoms deriving from case descriptions are partly separated from each other.

The semantic clean-up was the most laborious task, reducing over a thousand different symptoms to a few hundred. There was a risk of missing nuances in this process, but our main goal was to locate common symptoms. After the clean-up process, a pivot table indicated the frequency of each symptom and the number of medicines related to the symptom. From this, the LRs of each symptom for the respective medicines could be calculated, resulting in a 'mini-repertory' for three homeopathic medicines, see ►**Table 1**.

The 95% CI of some LRs is shown in ►**Table 2**. Statistical significance at a 95% level, however, is only partly related to clinical relevance.[8] In the present context, the fact that some LRs are statistically significant indicates that a sample containing at least 20 subjects who respond to a particular medicine gives reasonably accurate estimates.

There are significant differences between this mini-repertory and the well-known rubrics of the existing homeopathic repertory. Firstly, the entries are not based on absolute occurrence. This would have resulted in boldface typeface for most entries because of the repeated clinical confirmation. Secondly, the data for the three medicines are compared with each other and are only valid for COVID-19-like disease; the LRs are 'condition dependent'.[9] This can result in LRs of less than 1, indicating a relative contraindication. For example, the LRs below 1 linking *Ars* and *Bry* with 'fatigue' do not indicate that these medicines are *not* indicated for COVID-19 by this symptom, but rather that fatigue indicates *Gels* (LR = 1.62) more than average, whilst *Ars* (LR = 0.96) and *Bry* (LR = 0.77) are indicated less than average when the three prescribed medicines are compared. This mutual comparison of those medicines indicated by a disease is the third departure from the existing repertory. The result is that rather than simply giving boldface entries for all three medicines, this repertory is able to show a distinctive ordering of the three.

This ordering of individual symptoms can result in even larger differences between medicines when symptoms are combined by multiplying the respective LRs. ►**Table 3** shows composite LRs for three combinations of three symptoms. The composite LRs demonstrate that repertory entries based on LR values can differentiate medicines much better than

Table 1 Mini repertory for *Arsenicum*, *Bryonia* and *Gelsemium* regarding COVID-19-like illness. Symptoms are sub-rubrics for corresponding repertory rubrics, like 'HEAD – PAIN – COVID-19-like disease, in'

Symptoms	Total	*Ars*	LR *Ars*	*Bry*	LR *Bry*	*Gels*	LR *Gels*
	161	**21**		**45**		**25**	
Fatigue	87	11	0.96	20	0.77	20	1.62
Dry cough	73	8	0.82	26	1.43	10	0.86
Dyspnoea	51	5	0.72	18	1.41	4	0.46
Headache	48	6	0.95	17	1.41	9	1.26
Slow onset	46	6	1.00	14	1.13	9	1.32
Fever	46	3	0.47	15	1.25	9	1.32
Chill	42	5	0.90	13	1.16	14	2.72
Diarrhoea	35	8	1.98	10	1.03	6	1.13
Oppression chest	32	4	0.95	7	0.72	5	1.01
Throat pain	31	4	0.99	11	1.42	7	1.59
Muscle/bone pain	27	4	1.16	9	1.29	4	0.95
Chest pain	24	3	0.95	10	1.84	3	0.78
Anxiety	23	8	3.56	5	0.72	3	0.82
Loss of taste and/or smell	23	3	1.00	6	0.91		
Dry mouth	17	4	2.05	9	2.90	1	0.34
Thirst	16	2	0.95	9	3.31	2	0.78
Thirstless	15	1	0.48	4	0.94	5	2.72
Nausea	15	4	2.42	2	0.40	3	1.36
Back pain	13	1	0.56	8	4.12	1	0.45
Chest pain < cough	12	1	0.61	7	3.61	3	1.81
> Open air	11	1	0.67	4	1.47	1	0.54
Cough < talking	11	2	1.48	4	1.47		
Desire cold drinks	11			4	1.47	1	0.54
Cough < deep respiration	10	2	1.67	7	6.01		

Abbreviation: COVID-19, coronavirus disease 2019.

Table 2 95% confidence interval (95% CI) of some likelihood ratio (LR) values

Symptom	Medicine	LR	95% CI
Fatigue	*Gels*	1.62	1.252–2.106
Dry cough	*Bry*	1.43	1.022–1.990
Dyspnoea	*Bry*	1.41	0.888–2.227
Headache	*Bry*	1.41	0.874–2.287
Chill	*Gels*	2.72	1.684–4.392
Diarrhoea	*Ars*	1.98	1.040–3.753
Anxiety	*Ars*	3.56	1.722–7.343
Dry mouth	*Bry*	2.90	1.193–7.048

Abbreviations: Ars, *Arsenicum*; *Bry*, *Bryonia*; *Gels*, *Gelsemium*.

Table 3 Combined likelihood ratio (LR) of combinations of three symptoms

Combinations of symptoms	LR *Ars*	LR *Bry*	LR *Gels*
Diarrhoea + chill + anxiety	6.33	0.85	2.50
Dry cough + headache + back pain	0.43	8.31	0.49
Fatigue + chill + thirstless	0.41	0.83	12.01

Abbreviations: Ars, *Arsenicum*; *Bry*, *Bryonia*; *Gels*, *Gelsemium*.

the same based on absolute occurrence, thus making common symptoms more useful.

Let us assume that the (unknown) prior chance that any of the three medicines would work is 10%. A combination of three common symptoms could then raise this chance for a specific medicine to between 40 and 60%, further highlighting the contrast with the other medicines (see ►**Table 4**).

The systematic collection of treatment data and application of Bayes' theorem to calculate LRs allows relatively common symptoms to differentiate better between medicines, and this is enhanced by the combination of these symptoms. However, combining LRs requires a calculator, and it will be some time before computer-based repertories are able to perform the necessary calculations. To overcome this problem, authors TS, GI and LR have created an app that performs these calculations based on actual clinical data.

The app presents 20 symptoms for which LRs have been measured in COVID-19 cases, giving suggestions for eligible medicines from those symptoms chosen; with the currently available data, the medicines are currently confined to *Arsenicum*, *Bryonia* and *Gelsemium*. Symptoms were selected to be included in the app, which differentiated between these three medicines even if the LRs were not statistically significant. If data were not available, the LR was set at 1, giving neither an indication nor a contraindication.

Table 4 Effect of combined likelihood ratio (LR) values of ►**Table 3** on posterior chance, assuming a prior chance of 10%

Posterior chance with 10% prior chance	*Ars*	*Bry*	*Gels*
Diarrhoea + chill + anxiety	41%	9%	22%
Dry cough + headache + back pain	5%	48%	5%
Fatigue + chill + thirstless	4%	8%	57%

Abbreviations: Ars, *Arsenicum*; *Bry*, *Bryonia*; *Gels*, *Gelsemium*.

The app can be found with the following link: https://hpra.co.uk/. A print of the screen for symptom selection is shown in ►**Fig. 2**.

The app appears as a 'black box' with simply input and output, but that is only because it would be too complicated to show the full underlying algorithm and repertory rubrics. The app is based on the data shown in ►**Table 1**, published in the LMHI newsletter, and it shows a positive indication if the combined LR ≥ 3. As a rule of thumb, LR $= 3$ corresponds to a rise of posterior chance of about 20%. If the combined LR lies between 3 and 6, the medicine will appear in plain type; if combined LR is between 6 and 10, the medicine appears in italics; if combined LR ≥ 10 the medicine appears in boldface type.

Testing the App with Real Cases

A collection of case studies from Hong Kong (see reference 6) involving COVID-19 was published with 18 cases; these responded well to *Ars* (one case), *Bry* (four cases), *Gels* (12 cases) and *Eupatorium perfoliatum (Eup-p)* (one case).[6] The cases were presented with clear descriptions of background, symptomatology and outcome. This, as well as the fact that all cases except one responded to the medicines present in the app, offered an opportunity to test the app with the symptoms seen in these cases.

The comparison of the standard case taking and the app can be demonstrated by case HK1.1. The observed symptoms in the case taking were:

1. Slow onset and progression of symptoms.
2. Feeling irritable from the cough; does not want to talk to anyone. Prefers to be alone.
3. Obvious increase in thirst with desire to drink warm water in large quantity.
4. Generally ameliorated after perspiration.
5. Mainly dry cough, with very occasional greenish sputum.
6. Extremely bad pulsating headache in the temple, and middle chest pain aggravated from coughing.
7. Cough aggravated by talking and lying down, and after waking up in the morning.
8. Cough associated with tickling feeling in the throat, ameliorated by warm drinks.

Out of these eight complex symptom descriptions, consisting of 13 different single repertory symptoms, five single symptoms could be found in the app:

1. Thirst
2. Dry cough
3. Headache
4. Chest pain < cough
5. Cough < talking.

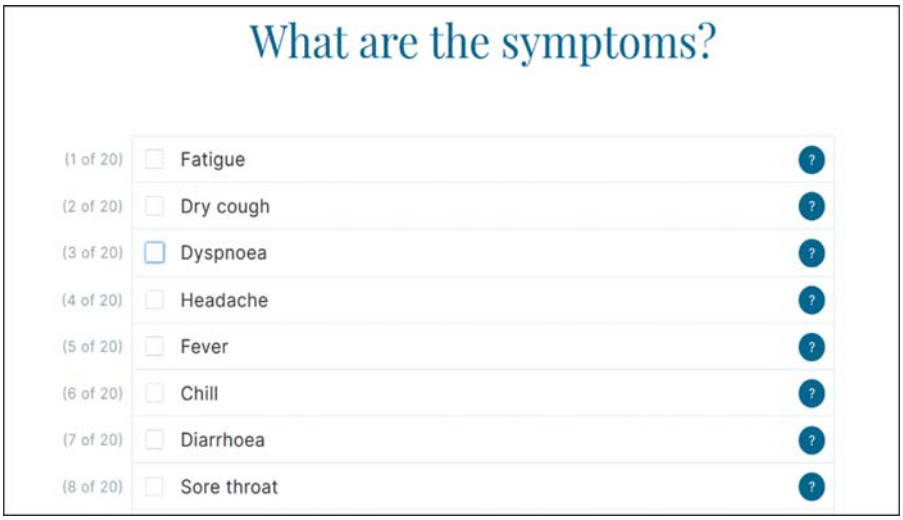

Fig. 2 Screenshot of the COVID-19 mini-repertory app. Explanation of symptoms could be obtained by clicking on the question mark to the right of the symptom.

The output of the app was 'Strong indication for Bryonia' and this was indeed the medicine that was prescribed by the clinician. An experienced homeopathic practitioner would probably recognise the medicine at first sight because of symptoms such as 'irritable from cough', 'aversion to company', 'thirst for large quantities' and 'headache from cough', which are not included in the app. However, with the combination of three symptoms, 'thirst', 'dry cough' and 'headache', the app would already have returned a 'Moderate indication for Bryonia'. This results from the following LRs for *Bry*: LR = 3.31 for thirst; LR = 1.43 for dry cough; and LR = 1.41 for headache. The combined LR for these three symptoms is $3.31 \times 1.43 \times 1.41 = 6.67$, high enough for a 'moderate indication'. 'Chest pain < cough' adds LR = 3.61 and 'Cough < talking' LR = 1.47, rendering a combined LR = 35.4, representing a strong indication.

The outcome of testing all cases is shown in ►**Table 5**. If the combined LR of the selected symptoms was between 3 and 6, the indication was 'slight'; if the combined LR was between 6 and 10, the indication was 'moderate'; and if combined LR > 10, the indication was 'strong'.

This set of cases contained only one case (HK5.5) that could not be handled by the app, because it contained no data for that particular medicine (*Eup-p*). In this case, the app gave only slight indications, but did not contradict the choice based on a full homeopathic evaluation by offering a moderate or strong indication for one of its own medicines.

In the remaining 17 cases, for 11 (65%) the recommendation of the app was entirely consistent with the full homeopathic evaluation, giving a moderate or strong indication for the prescribed medicine. In one case (HK5.2), a second medicine came up to the same degree; in this case, a specific symptom, 'coldness up and down the back' (not available in the app), clarified the choice of *Gels*. In three cases (HK2.1, HK4.2, HK4.3), the recommendation was consistent but with only a slight indication; it did not, though, contradict the definitive choice. In these cases, the full evaluation clarified the choice because of specific symptoms. In one case (HK5.4), the recommendation of the app slightly contraindicated the choice after standard case taking which was made on the basis of specific symptoms, such as 'Heaviness of the eyelids', which clearly indicated the prescribed medicine. In one other case (HK5.3) both the app and the repertorisation placed *Bry* first, but *Gels* was chosen on the whole picture. To summarise: in 16 out of 17 cases, the app made the same recommendation as the repertorisation, but using fewer symptoms and only common ones.

Discussion

The LMHI coordinated case collection from various sources in different formats, partly formatted as repertorisations, partly as pre-defined symptoms, and partly in free text format. In the course of this process, more information became available about common symptoms of the disease and contributors were guided by more pre-defined symptoms. Such a database can be an invaluable source of both qualitative and quantitative information. For this article, we focused on quantitative aspects, but the selection of suitable cases also required a qualitative analysis to identify those cases where a curative effect appeared likely. Amongst other factors, cases could not be used in this analysis where more than one homeopathic medicine had worked, as we sought to establish relationships between specific medicines and specific symptoms. Nevertheless, such cases can be useful in a more qualitative context. Cases where a causal relationship between improvement and the medicine was unclear were also excluded, but again these can be useful for other analyses, as can cases where there is no improvement.

Limitations of the Study

This data collection should be regarded as a learning project; it began with little knowledge about the disease-specific symptoms and with largely inexperienced contributors. There was no worked-out protocol and most symptoms were collected retrospectively. As the number of cases increased, directions

Table 5 Recommendations of the app after entering the symptoms available in 18 cases[6]

Case	Prescribed medicine	No. repertory symptoms	No. app symptoms	App advised medicine
HK1.1	*Bry*	13	5	*Bry* (strong)
HK2.1	*Bry*	22	5	*Bry* (slight)
HK3.1	*Bry*	26	6	*Bry* (strong)
HK3.2	*Gels*	16	5	*Gels* (strong), *Bry* (slight)
HK3.3	*Gels*	11	4	*Gels* (moderate)
HK3.4	*Gels*	14	3	*Gels* (strong)
HK3.5	*Gels*	15	6	*Gels* (strong), *Bry* (slight)
HK4.1	*Gels*	9	4	*Gels* (strong)
HK4.2	*Gels*	12	4	*Gels* (slight), *Bry* (slight)
HK4.3	*Ars*	9	4	*Ars* (slight), *Gels* (slight)
HK4.4	*Gels*	11	4	*Gels* (moderate)
HK4.5	*Gels*	11	4	*Gels* (strong)
HK5.1	*Gels*	9	4	*Gels* (strong)
HK5.2	*Bry*	13	6	*Bry* (moderate), *Gels* (moderate)
HK5.3	*Gels*	9	3	*Bry* (slight)
HK5.4	*Gels*	9	3	*Bry* (slight)
HK5.5	*Eup-p*	7	4	*Bry* (slight), *Gels* (slight)
HK6.1	*Bry*	25	8	*Bry* (strong)

Abbreviations: Ars, *Arsenicum*; *Bry*, *Bryonia*; *Gels*, *Gelsemium*.
Note: The 'No. repertory symptoms' is the number of symptoms described for each case. 'No. app symptoms' is the number of these symptoms available in the app. 'App advised medicine' represents the recommendation of the app (together with the strength of the recommendation).

for data collection were adjusted and communicated, and more symptoms were identified prospectively.

This analysis of observational data cannot be used as proof for the effectiveness of homeopathy. Whilst we made some effort to discard cases where a causal relationship between the medicine and improvement was unlikely, context effects and spontaneous recovery cannot be ruled out. False positive cases, where the improvement is caused by spontaneous recovery or context effects, result in an under-estimation of the LR.[10] On the other hand, the retrospective assessment of most symptoms could involve confirmation bias: some symptoms are well-known indicators for specific medicines, such as 'heaviness of eyelids' for *Gels*. Heaviness of eyelids was recorded in seven out of 25 *Gels* cases and not in the remainder of the population; it is possible that the symptom was present but remained unnoticed if *Gels* had not been considered. The risk of confirmation bias is greater in the case of keynote symptoms and this could cause over-estimation of LRs.[11]

A further potential bias arises from the fact that the multiplication of LRs assumes that these are independent, when in actuality some symptoms are correlated, and this could potentially give rise to artificially inflated LR products. An examination of the correlation matrix of the 20 symptoms using Pearson's contingency coefficient, C, revealed that of the 190 possible pair-wise correlations, most (158, 83.2%) were statistically non-significant, and of those that were significant, all were relatively small ($C \leq 0.26$) except one. This latter was between the symptoms 'Chest pain' and 'Chest pain aggravated by cough' ($C = 0.51$); as a result, 'Chest pain' was subsequently removed from the app, leaving 19 symptoms. Implementing a multivariate procedure in the app to eliminate this potential bias was beyond the scope of the current project, but it is intended to include this in future versions.

It is worth noting that this correlation between symptoms is also a problem in the existing repertory[12] and homeopathic practitioners have to handle this intuitively: e.g. they will be careful in combining symptoms where correlation can be expected, such as 'dry mouth' and 'thirst'. (In our data, these two symptoms showed a significant but relatively small correlation, $C = 0.20$.)

The urgency of this project prevented proper preparation and probably introduced some bias. Nevertheless, counting the prevalence of symptoms and estimating LR resulted in better differentiation between medicines with common symptoms, a differentiation that would be absent with the existing typology in repertory rubrics. The data collection showed that a very limited number of medicines appeared repeatedly in improved cases—*Ars*, *Bry* and *Gels* in 57.5% of all cases. These three medicines have a considerably higher prior chance of being curative than other medicines. Adding two or three further medicines might suffice for about 70% of all cases.

The reliability of the Bayesian mini-repertory with 20 common symptoms and three medicines, based on our data, has been tested with 18 real cases and showed results similar to conventional case-taking that relied on considerably more symptoms, both common and specific. We expect therefore that a Bayesian repertorisation using a limited number of common COVID-19 symptoms could improve the effectiveness of homeopathic COVID-19 treatment, especially if there are no specific symptoms to indicate particular medicines. This effectiveness could be further improved by adding two or three more medicines to the existing app after acquiring additional data.

The database underlying the app is derived from mostly mild cases. It is uncertain whether severe cases, for instance those with pneumonia, would respond to the same medicines. If it transpires that more severe cases are successfully treated with other homeopathic medicines the app must be adapted, or a separate app for severe (pneumonia) cases must be developed.

Conclusion

The pandemic outbreak of a new infectious disease offered the opportunity to develop new repertory rubrics of homeopathic symptoms *de novo*, using up-to-date statistical methods and worldwide data collection. Despite certain biases arising from the urgency of the project and the dynamic nature of adjustments to the protocol, important differences between LRs for

common symptoms for different medicines became apparent. For a reference set of cases, a computer algorithm based on LRs of 20 common symptoms and three medicines gave the same results as a full homeopathic evaluation, despite being based upon considerably fewer, and common, symptoms. This tool offers valuable support and more precise selection of medicines to the homeopathic practitioner.

Conflict of Interest

T. Smedley reports personal fees from LMHI Germany, during the conduct of the study, including his expenses for domain registration of the app. Dr. Gold serves as a consultant to Washington Homeopathic Products. Dr. Schroyens reports personal fees from Zeus Soft sprl, during the conduct of the study. Other authors report no conflict of interest.

Acknowledgements

We are very grateful to all those doctors who have contributed cases; it would be impossible to mention all their names. Not all their cases have been used for this evaluation, but those that remain can be used for other analyses. We thank Theodoros Lilas for his help in improving the spreadsheet.

References

1 World Health Organization. Coronavirus Disease COVID-2019. Situation Report Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
2 Coronavirus Disease 2019 (COVID-19). Symptoms pf Coronavirus Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed on June 5, 2020
3 Jacobs J. Homeopathic prevention and management of epidemic diseases. Homeopathy 2018;107:157–160
4 Ielciu I, Mouithys-Mickalad A, Franck T, et al. Flavonoid composition, cellular antioxidant activity and (myelo)peroxidase inhibition of a *Bryonia alba L.* (Cucurbitaceae) leaves extract. J Pharm Pharmacol 2019;71:230–239
5 Basu N, Das BC, Tandon S. Interim management of COVID-19 by repurposed homeopathic medicines. Homeopathy 2020;109: 182–183
6 To KLA, Fok YYY. Homeopathic clinical features of 18 patients in COVID-19 outbreaks in Hong Kong. Homeopathy 2020; 109:146–162
7 Federation of Medical Scientific Societies. Code of Conduct for Medical Research. Available at: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/codes-of-conduct/code-of-conduct-for-medical-research
8 Rutten ALB, Stolper CF, Lugten RFG, Barthels RWJM. Statistical analysis of six repertory rubrics after prospective assessment applying Bayes' theorem. Homeopathy 2009;98:26–34
9 Miglani A, Rutten L, Manchanda RK. Generalisability of prognostic factor research: further analysis of data from the IIPCOS2 study. Homeopathy 2017;106:155–159
10 Rutten ALB, Stolper CF, Lugten RF, Barthels RW. 'Cure' as the gold standard for likelihood ratio assessment: theoretical considerations. Homeopathy 2004;93:78–83
11 Rutten ALB, Stolper CF. Diagnostic test evaluation by patient-outcome study in homeopathy: balancing of feasibility and validity. J Eval Clin Pract 2009;15:1230–1235
12 Rutten L, Van Wassenhoven M. Clinical verification of homeopathic symptoms: experience and statistics. In: Bonamin L, ed. Signals and Images. Springe Science + Business Media; 2008:151–182