Correlation between work impairment, scores of rhinitis severity and asthma using the MASK-air® App

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Correlation between work impairment, scores of rhinitis severity and asthma using the MASK-air® App

Original article

Short title: Scores in rhinitis and asthma using an mHealth app

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<table>
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<tr>
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<td>19.</td>
<td>Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico.</td>
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<td>20.</td>
<td>Sachs’ Children and Youth Hospital, Södersjukhuset, Stockholm and Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.</td>
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<tr>
<td>21.</td>
<td>Department of Medical Sciences, Allergy and Clinical Immunology Unit, University of Torino &amp; Mauriziano Hospital, Torino, Italy.</td>
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<td>Institute of Medical Statistics, and Computational Biology, Medical Faculty, University of Cologne, Germany and CRI-Clinical Research International-Ltd, Hamburg, Germany.</td>
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<td>23.</td>
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<td>Division of Infection, Immunity &amp; Respiratory Medicine, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK.</td>
</tr>
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<td>Department of General ORL, H&amp;NS, Medical University of Graz, Austria.</td>
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<td>28.</td>
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<td>University Hospital, Montpellier, France.</td>
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<tr>
<td>32.</td>
<td>INSERM U 1168, VIMA : Ageing and chronic diseases Epidemiological and public health approaches, Villejuif, Université Versailles St-Quentin-en-Yvelines, UMR-S 1168, Montigny le Bretonneux, France, Euforea, Brussels, Belgium, and Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.</td>
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Abstract

Background: In allergic rhinitis, a relevant outcome providing information on the effectiveness of interventions is needed. In MASK-air (Mobile Airways Sentinel Network), a visual analogue scale (VAS) for work is used as a relevant outcome. This study aimed to assess the performance of the work VAS work by comparing VAS work with other VAS measurements and symptom-medication scores obtained concurrently.

Methods: All consecutive MASK-air users in 23 countries from June 1, 2016 to October 31, 2018 were included (14,189 users; 205,904 days). Geolocalized users self-assessed daily symptom control using the touchscreen functionality on their smart phone to click on VAS scores (ranging from 0 to 100) for overall symptoms (global), nose, eyes, asthma and work. Two symptom-medication scores were used: the modified EAACI CSMS score, and the MASK control score for rhinitis. To assess data quality, the intra-individual response variability (IRV) index was calculated.

Results: A strong correlation was observed between VAS work and other VAS. The highest levels for correlation with VAS work and variance explained in VAS work were found with VAS global, followed by VAS nose, eye and asthma. In comparison to VAS global, the mCSMS and MASK control score showed a lower correlation with VAS work. Results are unlikely to be explained by a low quality of data arising from repeated VAS measures.

Conclusions: VAS work correlates with other outcomes (VAS global, nose, eye and asthma) but less well with a symptom-medication score. VAS work should be considered as a potentially useful AR outcome in intervention studies.

Key words: asthma, rhinitis, MASK, Visual analogue scale, score
Abbreviations

AR: allergic rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
CSMS: combined symptom and medication score
EAACI: European Academy of Allergy and Clinical Immunology
EQ-5D: EuroQuol
ICT: information and communications technology
IER: Insufficient effort responding
IRV: Intra-individual response variability
MASK: Mobile Airway Sentinel NetworK
SMS: Symptom-medication score
VAS: visual analogue scale

Introduction

In allergic rhinitis (AR) and asthma, a relevant outcome providing information on the cost-effectiveness of interventions is needed. EQ-5D, a validated measure of quality of life, has been used in AR (1-7) but it cannot be assessed daily.

MASK-air (Mobile Airways Sentinel NetworK) is an information and communication technology (ICT) system centred around the patient (online supplement) (8-13) and operational in 23 countries. It uses a treatment scroll list which includes all medications customized for each country as well as visual analogue scales (VASs) to assess global allergy, rhinitis, eye and asthma control. Over 30,000 users and 250,000 VAS days have been recorded. A pilot study found a highly significant correlation between VAS work and other VAS measurements (global, nose, eyes and asthma) (14).

Symptom-medication scores (SMSs) are also needed to investigate the effect of AR treatments, in particular allergen immunotherapy (AIT) (15). The European Academy of Allergy and Clinical Immunology (EAACI) has defined the combined symptom and medication score (CSMS) for AIT trials (16).

Surveys collect information but data quality is a concern: in particular, insufficient effort responding (IER), a phenomenon by which respondents try to complete the questionnaire with the shortest time without providing reliable information (17). This can result in respondents providing the same value for all questions, which will artificially increase the correlation between items (18). Several methods are used to assess data quality including the intra-individual response variability (IRV) index, a flexible way to detect IER (17).
This study aimed to compare VAS work with other VAS measurements and SMSs obtained concurrently. In order to investigate data quality, we also assessed the IRV index (17).

**Methods**

**Users**

All consecutive MASK-air users from June 1, 2016 to October 31, 2018 were included with no exclusion criteria, according to methods previously described (19-21). MASK-air® was used by people who found it on the internet, Apple store, Google Play or in any other way. Some users were clinic patients who were asked by their physicians to use the app. This was the case for the transfer of innovation project (22). However, due to anonymization of data, no specific information could be gathered, as previously described in detail (19, 23).

**Setting**

Users from 23 countries filled in the MASK-air Allergy Diary (Table 1).

**Ethics**

The Allergy Diary is CE1. CE marking indicates conformity with health, safety, and environmental protection standards for products made in the EU and meets the essential requirements of all relevant European Medical Device Directives (24). The data were anonymized. An independent Review Board approval was not required since the study is observational and users agreed to have their data analysed (terms of use).

**MASK-air® and outcomes**

Geolocalized users self-assessed daily symptom control using the touchscreen functionality on their smartphone to click on VAS scores (ranging from 0 to 100) for overall symptoms (global), nose, eyes, asthma and work - asked in this order - with several other screens in between (Figure 1 online). Users input their daily medications using a scroll list containing all country-specific OTC and prescribed medications for each country.

Two SMSs were used: the modified EAACI CSMS score (16), accounting for a new medication that did not exist when it was devised (Table 2), and the MASK control score for rhinitis proposed according to existing data (13) (Table 3). Medications considered in the study are detailed in online Table 1.

**Statistical methods and analyses**

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A non-Gaussian distribution was found for the data. Non-parametric tests and medians (and percentiles) were used. Some users reported VAS scores more than once a day and we used the highest level (13).

For each score, we calculated and compared: (i) the within-subject correlation with VAS work (calculated using fixed-effect models using the Stata xtreg command) and (ii) the variance explained in VAS work (which corresponds to the correlation measured in (i) squared). Only person-days with a reported VAS work were tested. Differences in correlations by gender, age (above versus below median age – i.e. 32 years-old) and season (pollen season – i.e. from March 15 to the end of June, versus the period outside pollen season – i.e. from August to December) were investigated. Regarding VAS asthma, since not all users are asthmatic, a lot of non-asthmatic users will fill in a VAS asthma of 0 (no missing information is allowed) when using the app. Therefore, differences in the correlation between VAS work and VAS asthma by asthma status were investigated.

The intra-individual response variability (IRV) index was calculated, based on answers to the five VAS scores, to detect IER (17). All person-days were tested. The IRV is the standard deviation of responses across a set of consecutive item responses for an individual. It is an indicator of insufficient effort responding.

The number of days of reporting per user was examined and a Mann–Whitney U test was used to make comparisons in countries where physicians were including patients using the transfer of innovation (Twinning) project (22) and in countries where this was not the case. This analysis was repeated after excluding countries with low numbers of users (e.g. Canada and Czech Republic).

**Results**

**Users**

The study included 14,189 users and 205,904 days (Table 1). Approximately 5% of users did not report their age or reported an age below 10. Users ranged in age from zero to 92 years (mean, SD: 32.1 ± 15.3 years). There were 55.3% women and 44.7% men. 98,303 days were tested for VAS work correlations. In this group, there were 53,241 (54.2%) days without treatment (Figure 1).

**Main results**

A strong correlation was observed between VAS work and other VAS (Table 4). The highest levels for correlation with VAS work and variance explained in VAS work were found with VAS global,
followed by VAS nose, eye and asthma. In comparison to VAS global, the mCSMS and MASK control score showed a lower correlation with VAS work and explained less variance in VAS work.

The within-subject correlation between VAS work and VAS global did not vary by age, gender or season. For the other outcomes, the within-subject correlation with VAS work did not vary substantially between males and females (i.e. difference of less than 5%) or between days recorded during and outside the pollen season (i.e. difference of less than 4%). When we stratified by median age (i.e. 32 years-old), the correlation varied the most between VAS work and VAS eyes (i.e. within-subject correlations of 0.60 for days recorded by older users and 0.52 for days recorded by younger users) and between VAS work and VAS asthma (i.e. within-subject correlations of 0.48 for days recorded by older users and 0.40 for days recorded by younger users).

The within-subject correlation between VAS work and VAS asthma was higher in days recorded by users who reported asthma when they started using the app, compared to days recorded by users who did not report asthma ($r=0.54$ vs 0.38).

**Intra-individual response variability**

Of the 205,904 person-days, there was no variability in 35,592 days (17.3%) (users respond with the same value to all five VAS). 35,373 (99.4%) of them corresponded to a value of zero (no symptoms) answered to all questions. Without counting person-days with all variables at zero, 48,086 person-days (23.4%) had an IRV ≤3.6 (Table 5). An IRV of 3.6 implies a difference of up to 10 points (on a 0-100 point scale) in at least one of the VAS measures.

As a post hoc analysis, we recalculated the correlations with VAS work and variances explained in VAS work, after excluding person-days with low intra-individual response variability (i.e. defined as IRV ≤3.6) and similar results were obtained (online Table 2).

**Number of days of reporting**

The number of days of reporting per user was significantly greater in countries where a transfer of innovation was carried out than in those that did not perform this project ($p$ for Mann–Whitney U test =0.0001) (Table 1). When this analysis was repeated after excluding countries with low numbers of users (e.g. Canada and Czech Republic), the difference remained highly statistically significant ($p$ for Mann–Whitney U test<0.0001).
Discussion

The strengths of the study are the sample size and the wide distribution of users in 23 countries and 17 languages. There is one strong message and two extra messages. First, there is a high correlation between VAS work and rhinitis control assessed by VAS global or nose. Second, the strong correlations we observed between VAS work and other VAS scores are unlikely to be explained by a low quality of data arising from repeated VAS measures. Third, in comparison to VAS global, the two SMSs showed a lower correlation with VAS work, and explained less variance in VAS work.

Our results are unlikely to be explained by a low quality of data arising from repeated VAS measures: (i) VAS work is the last VAS measure assessed, and it is measured after 5 screens without any VAS question, which makes it more difficult to reproduce the previous VAS (Figure 1 online); (ii) Correlations differ between outcomes; (iii) Over 99% of the person-days with no variation in the five VAS measures corresponded to a value of zero answered to all of them, which is plausible in days with no symptoms; (iv) A very low variability in VAS measures was assessed by taking a cutoff of IRV index below 3.6. Although other cutoff values could be used, this represents a realistic maximal difference of 10 points on a 0-100 point scale of some of the VAS measures. Only 23.4% of person-days had a low variability in the response to several questions and were suspected of engaging in IER. However, this is an upper bound, as low variability in responses is actually possible in reality (i.e. on days in which the patient has the same or similar degree of impairment for all questions); (v) The strong correlations found between the different scores and VAS work were not substantially reduced when person-days with low intra-individual response variability were excluded from the analyses, suggesting that they are not “artificially” driven by IER.

In order to determine the relative cost-effectiveness of new interventions, many countries propose to conduct a health economic evaluation either by adopting a health care perspective only or by adding a societal perspective aiming to include all relevant effects and costs (25). Productivity costs are frequently omitted from economic evaluations, despite their often strong impact on cost-effectiveness outcomes, partly because of the lack of standardization regarding the methodology of estimating productivity costs (26). Allergic rhinitis impairs quality-of-life (27) but never induces death. Thus the Decision Analytic Modelling (DAM) model may be difficult to apply (28). EQ5D is impaired in severe AR whereas work productivity is often impaired in moderate AR (29). Thus, VAS work may be a more sensitive surrogate end point to assess the economic evaluation of an intervention in AR. Moreover, a daily assessment of work productivity can be carried out with VAS. Using the novel feature of MASK, the integration of pollen season and air quality the same day as VAS work will provide a very sensitive outcome on health economics for clinical trials. In clinical practice, VAS global may be more relevant. To our knowledge, limitations of real-word data using an app are the...
same for all VAS measurements. VAS work validation was not done since this criterion was not included in the first version of the app.

In comparison to VAS global, the two SMSs showed a lower correlation with VAS work, and explained less variance in VAS work. This is probably because we used simple methods to assess SMSs and more sophisticated analyses are needed. In particular, it seems that adding the same coefficient to a symptom score or a VAS level may not be optimal. From the real-world evidence from MASK (13, 21), it appears that (i) medications may have a different efficacy depending on rhinitis control level: higher impact for a lower VAS level and lower impact for a higher VAS level and (ii) co-medication may be considered. New SMS are therefore needed.

One of the major problems with apps is the low adherence to their use. Achieving sufficient mHealth App engagement and user retention rates is a difficult task. In MASK, over 50% of the users use the app only once. Differences in the duration of reporting were found. It is clear that in countries where many patients have been enrolled by physicians during a transfer of innovation, the duration of reporting is longer than in countries where this protocol was not used. This information should be carefully considered to increase adherence to MASK use.

**Generalisability**

The data obtained were retrieved from 23 countries. Although there was no specific study in the different countries, the results appear generalizable.

**Conclusion**

This study suggests that VAS work can be used as a surrogate end-point for the assessment of health economics in rhinitis and that symptom medication scores tested with real-world data need to be improved.

**Statement of author contribution :**

A Bédard, JM Anto, JA Fonseca, X Basagana and J Bousquet conceived the study and drafted the manuscript. A Bédard and X Basagana conducted the statistical analyses. O Pfaar and J Bousquet designed the symptom-medications scores used in the analyses. All authors reviewed the study design and the manuscript and have approved the final version of the manuscript".

**Conflicts of Interest :**

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Dr. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work.

Dr. Bosnic-Anticevich reports grants from TEVA, personal fees from TEVA, AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, Mylan, outside the submitted work.

Dr. Cardona reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Diater, LETI, Thermofisher, Stallergenes, outside the submitted work.

Dr. Fonseca being a partner in a company developing mobile technologies for monitoring airways diseases

Dr. Hellings reports grants and personal fees from Mylan, during the conduct of the study; personal fees from Sanofi, Allergopharma, Stallergenes, outside the submitted work.

Dr. Ivancevich reports personal fees from Faes Farma, Eurofarma Argentina, other from Sanofi, Laboratorios Casasco, personal fees from, outside the submitted work.

Dr. Kuna reports personal fees from Adamed, AstraZeneca, Boehringer Ingelheim, Hal, Chiesi, Novartis, Berlin Chemie Menarini, outside the submitted work.

Dr. Kvedariene reports personal fees from GSK, non-financial support from StallergenGreer, Mylan, AstraZeneca, Dimuna, Norameda, outside the submitted work.

Dr. Larenas Linnemann reports personal fees from Amstrong, Astrazeneca, Boehringer Ingelheim, Chiesi, DBV Technologies, Grunenthal, GSK, MEDA, Menarini, MSD, Novartis, Pfizer, Novartis, Sanofi, Siegfried, UCB. grants from Sanofi, Astrazeneca, Novartis, UCB, GSK, TEVA, Boehringer Ingelheim, Chiesi outside the submitted work.

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Dr. Papadopoulos reports personal fees from Novartis, Nutricia, HAL, MENARINI/FAES FARMA, SANOFI, MYLAN/MEDA, BIOMAY, Astrazeneca, GSK, MSD, ASIT BIOTECH, Boehringer Ingelheim, grants from Gerolymatos International SA, Capricare, outside the submitted work.

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References


Table 1: Number of users recording Visual Analogue Scale score using MASK-air® by country

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<th>Country</th>
<th>Number of Days</th>
<th>Number of Users</th>
<th>Number of days per user (median, p25-</th>
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<td>Netherlands</td>
<td>7,509</td>
<td>944</td>
<td>2 [1-5]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>10,295</td>
<td>914</td>
<td>2 [1-6]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>11,310</td>
<td>1,506</td>
<td>2 [1-4]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>14,880</td>
<td>771</td>
<td>4 [1-17]</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>1,359</td>
<td>131</td>
<td>2 [1-7]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>3,955</td>
<td>815</td>
<td>1 [1-2]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>2,595</td>
<td>238</td>
<td>2 [1-5]</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>5,021</td>
<td>522</td>
<td>2 [1-8]</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Total | 205,904 | 14,189 |

**Table 2: Definition of the modified EAACI CSMS**

\[ mCSMS = \frac{\text{Symptom Score} + \text{Medication Score}}{2} \]

where Symptom Score is the 0-100 global VAS score, and Medication Score is a 0-100 score depending on the medication taken. For the latter, we used the following proposed scoring system:
- no medication = 0 points;
- oral non-sedative H1 antihistamines (H1A) lone = \(100 \times \frac{1}{4} = 25\) points;
- intra-nasal corticosteroids (INCS) – except Azelastine-Fluticasone Propionate combination (MPAzeFlu) - with/without H1A = \(100 \times \frac{2}{4} = 50\) points;
- MPAzeFlu = \(100 \times \frac{3}{4} = 75\) points;
- oral corticosteroids with/without INCS, with/without H1A, with/without MPAzeFlu = 100 points.

Table 3: Definition of the MASK rhinitis control score

The MASK rhinitis control score was equal to 1 if:

1. VAS global \(\geq 50/100\)
   or
2. VAS global \(\geq 35\) with the use of INCS-containing medication
   or
3. VAS global \(\geq 20\) with the use of at least 3 medications

The MASK rhinitis control score was equal to 0 otherwise.
Table 4. Within-subject correlations between VAS work and other rhinitis scores

<table>
<thead>
<tr>
<th>Number of days</th>
<th>Continuous scores</th>
<th>Binary score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, 25-75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(continuous outcomes) or</td>
<td>VAS global</td>
<td>VAS nose</td>
</tr>
<tr>
<td>% (binary outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td><strong>Within-subject correlation</strong></td>
<td>98,303</td>
<td></td>
</tr>
<tr>
<td>with VAS work</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Variance explained in VAS</strong></td>
<td>98,303</td>
<td>0.53</td>
</tr>
<tr>
<td>work</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 5. Intra-individual response variability (i.e. based on answers to the five VAS scores)

<table>
<thead>
<tr>
<th>IRV</th>
<th>Number of person-days</th>
<th>Example of VAS values in a representative patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.44</td>
<td>2,422</td>
<td>One of the VAS measures differs in 1 unit (i.e. on a 0-100 point scale) from the rest. E.g. providing the following values for the five VAS measures: (0,0,1,0,0)</td>
</tr>
<tr>
<td>0.5</td>
<td>2,622</td>
<td>One of the VAS measures differs in 1 unit from the rest (among person-days that have one missing value) E.g. providing the following values for the five VAS measures: (0,0,1,0,missing)</td>
</tr>
<tr>
<td>0.548</td>
<td>1,003</td>
<td>Two VAS measures differ in 1 unit from the rest. E.g. providing the following values for the five VAS measures: (8,7,8,8,7)</td>
</tr>
<tr>
<td>1</td>
<td>1,330</td>
<td>Variations of 3 units among the VAS measures E.g. providing the following values for the five VAS measures: (42,41,42,40,40)</td>
</tr>
<tr>
<td>1.5</td>
<td>1,431</td>
<td>One of the VAS measures differs in 3 units from the rest (among person-days that have one missing value) E.g. providing the following values for the five VAS measures: (22,22,19,22,missing)</td>
</tr>
<tr>
<td>2</td>
<td>690</td>
<td>Variations of 5 units among the VAS measures. E.g. providing the following values for the five VAS measures: (26,24,27,22,26)</td>
</tr>
<tr>
<td>3.6</td>
<td>44</td>
<td>Variations of up to 10 units among the VAS measures. E.g. providing the following values for the five VAS measures: (56,52,50,51,46)</td>
</tr>
</tbody>
</table>

**Total ≤3.6 = 48,086 (23.4%)**

*: not counting person-days with all 0 values

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**Figure 1. Flow chart of the study population**

MASK Study group

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46. Argentine Association of Respiratory Medicine, Buenos Aires, Argentina.
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211,003 VAS recorded between January 1, 2016 and December 31, 2018

- 5,099 duplicates or multiplicates

205,904 single VAS days recorded between 2016 and 2018 (14,189 users)

- 107,601 days without VAS work

98,303 single VAS days recorded between 2016 and 2018 with VAS work

53,241 days without treatment
45,062 days with treatment

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