

LETTER

Development of the EAACI% season definition a backup for a global application

To the editor,

Pollen seasons progress differently in their timing, course, and intensity in different countries/biogeographical regions depending on regional factors such as vegetation, elevation, urbanization, and others. The variable regional situation often provides obstacles for a standard season definition.¹ The season definition of the European Academy of Allergy and Clinical Immunology (EAACI) was published as a pollen concentration season definition depending on the selected pollen type reaching a certain threshold after a certain period of consecutive days,^{2,3} and it was demonstrated that they can be correlated with pollen-induced symptom loads.⁴ The season definition was developed for studies with a medical framework, particularly to allow a prospective approach. However, pollen concentrations do not reach the same level in Europe or globally and affect persons concerned differently.⁵ Therefore, there is a strong need to expand the scope of application of the EAACI season definition to a retrospective approach if the standard season definition criteria are not met within the site selection or during a clinical trial.

Hence, we tried to transfer the EAACI season definition criteria into a percentage definition (EAACI%) for birch and grasses in a first approach herein to include areas where the pollen concentrations do not meet the criteria of the EAACI season definition or small gaps in the data record prevent an EAACI season definition result. For this “backup” season definition, ten pollen monitoring stations across central and eastern Europe were used as the calculation basis for transforming the EAACI season definition.

A cumulative relative pollen concentration (r_d) was calculated for the start, end and peak days of the standard EAACI season definition applying the following formula:

$$r_d = \frac{\sum_{i=1}^d p_i}{\sum_{i=1}^{365} p_i}$$

Summarized, the cumulative pollen concentration (p_i) from the first day of the year to day d is divided by the yearly total sum of the respective pollen type.

For further optimization, these values were calculated for all sites, pollen types, and years to minimize the mean absolute deviation in comparison with the standard EAACI definition.

This calculation results in four percentage values (v) per pollen type, which define the start and the end of the (peak) pollen season. If the relative cumulative pollen concentration exceeds one of the thresholds (v), the respective date marks the (peak) pollen season start/end of the EAACI% definition. For the result validation, the difference in the season's duration was compared with each of the definitions applied (Table 1).

Additional information regarding the methodology and results as well as a calculation example can be found in the Appendix S1. To evaluate the EAACI% season definition, the Austrian pollen monitoring site of Tamsweg (ATTAMS) was selected as an experimental station to compare both season definitions and to test the application to data, where the EAACI season definition fails (Figure 1).

This first attempt demonstrates that the EAACI season definition criteria could successfully be converted into a percentage definition. We recommend using the herein described EAACI% season definition for predictive assistance in site selection or retrospective analysis in sites/countries where the EAACI season definition could not be applied during an ongoing trial. This transformed definition allows an accurate assessment of the pollen season using EAACI criteria in terms of start and end of the pollen season where the EAACI season definition would fail. A moving average season definition usually used in trend analysis, could improve the results of this definition in the future approaches.⁶ Taking together this

TABLE 1 Calculated thresholds of the EAACI% definition for birch ($v_{b,s}$) and grasses ($v_{g,s}$) for the start of the main pollen season ($v_{a,1}$), the end of the main pollen season ($v_{a,2}$), the start of the peak pollen season ($v_{a,3}$), and the end of the peak pollen season ($v_{a,4}$)

	Main season start ($v_{a,1}$)	Main season end ($v_{a,2}$)	Peak season start ($v_{a,3}$)	Peak season end ($v_{a,4}$)
Birch ($v_{b,s}$)	$v_{b,1} = 0.013$ 2 (1–2 days)	$v_{b,2} = 0.968$ 6.4 (2–10 days)	$v_{b,3} = 0.081$ 1.8 (1–3 days)	$v_{b,4} = 0.868$ 3.1 (1–5 days)
Grass ($v_{g,s}$)	$v_{g,1} = 0.016$ 4.7 (2–6 days)	$v_{g,2} = 0.962$ 13.2 (5–21 days)	$v_{g,3} = 0.182$ 3.6 (1–7 days)	$v_{g,4} = 0.683$ 7.4 (2–13 days)

Note: In addition, the mean absolute deviation for all stations and years as a comparison to the standard EAACI season definition is displayed, including the 25% and 75% quantiles in brackets.

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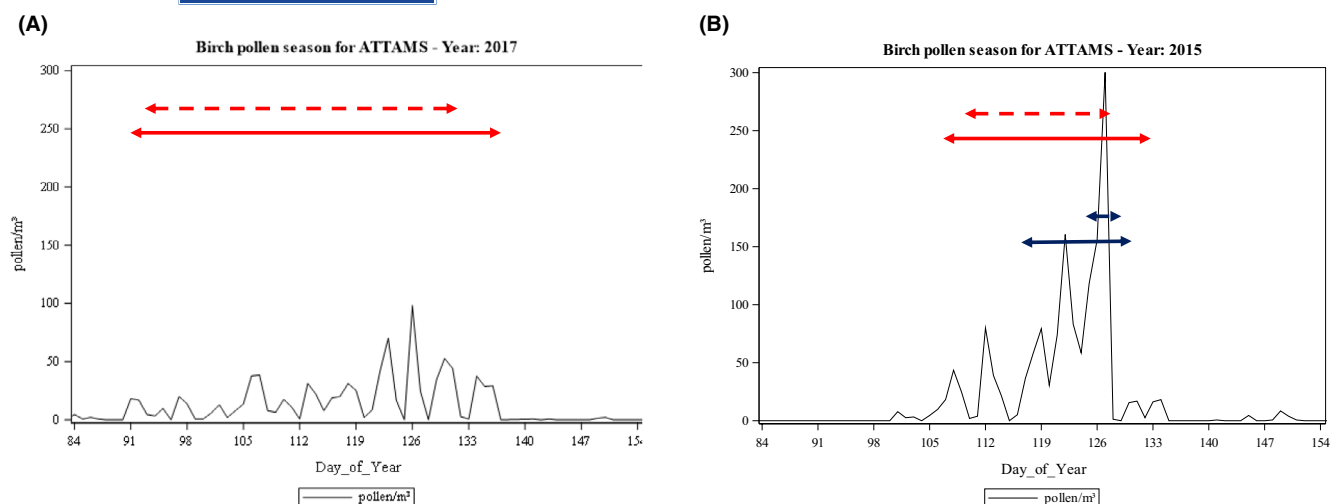


FIGURE 1 Course of the birch pollen season of the station Tamsweg (Austria) for the years 2015 and 2017. (A) Neither the main pollen season, nor the peak pollen season could be derived from the EAACI definition (no matching criteria), but only from EAACI% definition. (B) Both season definitions could be applied. The solid lines display the start and the end of the main pollen season and dashed lines the peak pollen season. The blue lines show the ranges of the EAACI season definition whereas the red lines display the ranges of the EAACI% definition

calculation may be helpful in trial regions of interest with low pollen concentrations, an exceptional less intense season, or other possible obstacles for pollen concentration-based season definitions. However, further validation with clinical data from hayfever patients is needed.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix S2

Additional information for the methodology of the EAACI% season definition

In this first trial, the birch and the grass pollen seasons from 2015 to 2019 from one station of Austria (ATWIEN), one station of Belgium (BEBRUS), one station of Czech Republic (CZBRNO), three stations of Germany (DEBER1, DEFULD, DEMOEN), one station of Croatia (HRZAGR), one station of Hungary (HUPEST), one station of Poland (PLLODZ) and one station of Serbia (RSBEL1) were used to calculate an EAACI% definition that approximates the EAACI definition best (more than 10000 data points).

The following criteria for the stations were used to be included into the calculation:

- Possible implementation of the EAACI season definition for the birch and the grass pollen season
- Possible implementation of the EAACI peak pollen season definition for the birch and the grass pollen season
- Preferably complete time series without or only a few gap days in the data track
- The best data quality possible and working after European standards (EN16868:2019 09 01)

Station codes

ATWIEN – Vienna (Austria)

BEBRUS – Brussels (Belgium)

CZBRNO – Brno (Czech Republic)

DEBER1 – Berlin (Germany)

DEFULD – Fulda (Germany)

DEMOEN – Mönchengladbach (Germany)

HRZAGR – Zagreb (Croatia)

HUPEST – Budapest (Hungary)

PLLODZ – Lodz (Poland)

RSBEL1 – Belgrad (Serbia)

The following calculation example for the birch pollen season explains the formula from the main document and the transformation from the EAACI season definition into the EAACI% definition. For our approach the original EAACI season definition was applied for the example data set by the daily mean pollen concentrations for (peak) season start/end (column 2). The respective day refers to a specific absolute cumulative pollen concentration (column 3) for the whole example year. This absolute cumulative pollen concentration is then divided by the yearly total pollen amount which results in a cumulative relative pollen concentration (column 4) and the respective percentage values for start/end of the (peak) pollen season (EAACI%). This process was performed for all reference pollen monitoring stations and years including an optimization process to average the data to come to the final calculation from the main document (see Table 1).

Day of Year	Daily mean pollen concentration	Absolute cumulative pollen concentration	Relative cumulative pollen concentration
1-70	-	2.04	0.000
71	0.00	2.04	0.000
72	3.00	5.04	0.001
73	2.00	7.04	0.001
74	1.00	8.04	0.001
75	2.00	10.04	0.001
76	2.00	12.04	0.002
77	6.00	18.04	0.002
78	9.00	27.04	0.004
79	45.00	72.04	0.009
80	468.00	540.04	0.071 $\geq$ 0.013
	(Season Start EAACI)		(Season Start EAACI%)
81	209.50	749.54	0.099
82	95.50	845.04	0.111
83	82.50	927.54	0.122
84	38.50	966.04	0.127
85-115	-	7203.54	0.948
116	95.50	7299.04	0.961
117	10.50	7309.54	0.962
118	21.00	7330.54	0.965
119	21.50	7352.04	0.968 $\leq$ 0.968
	(Season End EAACI)		(Season End EAACI%)
120	28.50	7380.54	0.972
121	14.00	7394.54	0.973
122	16.50	7411.04	0.976
123	9.00	7420.04	0.977
124	7.50	7427.54	0.978
125	6.00	7433.54	0.979
126-365	-	7595.88	1.000

Table 2: Calculation example for the birch pollen season. The respective day of the year, the daily mean pollen concentration, the absolute cumulative pollen concentration and the relative cumulative pollen concentration is displayed. The season start/end of the EAACI season definition and the referring percentage values from the relative cumulative pollen concentrations are marked in dark green. The season duration is marked in light green.

Additional information to the results

The intension of the described algorithm to define peak and main pollen season is to enable a calculation retrospectively even if the thresholds of the standard EAACI season definition are not reached within a study. This might happen if (1) the pollen concentrations are not high enough to meet the criteria of the EAACI (peak) season definition (although a pollen season is present) or (2) smaller gaps in the data track prevent a proper application of the season definition (especially for the season start). The EAACI% definition works with a cumulative daily approach. This means if a certain relative cumulative sum per day ($v_{a,s}$) (Table 1) is exceeded the main pollen season start, the main pollen season end, the peak

pollen season start or the peak pollen season end is announced. On the other hand, the EAACI season definition uses absolute pollen concentrations to derive these thresholds. The absolute pollen concentrations do not impact the application of the EAACI% definition, only the calculated relative values that make this season definition applicable if one of the cases mentioned above occurs.

The main difference in the results is the mean absolute deviations between the grass pollen and the birch pollen season. While the absolute deviations for the birch pollen season are below one week for every threshold, the grass pollen season deviations are higher, especially at the end of the main grass pollen season may amount to 21 days (Table 1).

These differences can be explained in two ways. Firstly, the grass pollen season is longer than the birch pollen season and therefore also the variance in the mean absolute deviations is higher. Secondly, the grass pollen season consists of various species, while the birch pollen season only refers to a single (or a couple of) species. Hence, the grass pollen season is far more complex since different grasses flower at different times within the season producing several peaks, which will affect the results.

The example of the pollen monitoring station Tamsweg supports the application of the EAACI% definition if the criteria of the EAACI season definition are not met (Figure 1A), but also if the EAACI season definition works (Figure 1B). Differences of the main pollen season start/end comparing both definitions are clearly visible (season start 11 days, season end five days) and should be compared with clinical data to improve the percentage transformation from the EAACI season definition. However, the peak pollen season is covered more accurately with the EAACI% definition (four peaks included; 20 days in total) than with the EAACI peak season definition (only one peak included, three days in total). The main pitfall of the EAACI% definition is the retrospective approach which makes the definition inapplicable to prospectively define the start of the season in a clinical trial. However, the EAACI% definition should not replace the EAACI season definition but extend the range of this definition to regions/years which do not meet the EAACI season definition criteria during a trial or a site/region/continent of interest (see Figure 1A). Therefore, this approach should be seen as a backup opportunity once the end of the pollen season is confirmed but does not meet the EAACI season definition criteria. Moreover, clinical trials depend not only on actual pollen data but also on a predictive site selection at the beginning of a clinical trial based on historical data, which is another possibility for applying the EAACI% definition. In most cases, a cumulative relative pollen concentration between 95-97% is acceptable to determine reasonable thresholds, so the season definition does not require a complete year of data but only local expertise or adequate forecasts to be applied shortly after the respective pollen season.

Limitations:

The current approach is limited to the pollen types of birch and grasses and therefore only covers a part of the EAACI standard season definition. Pollen types such as cypress and olive tree, which are also included in the EAACI season definition, need a different set of study centers, since they are limited to the Mediterranean and southeastern parts of Europe. The stated site selection criteria are necessary to produce a solid data fundament as well as the respective results for further evaluation and need to be adapted for every pollen type and the respective study approach. Therefore, the definition proposed will not be valid for all cases and pollen types and has room for improvement in future approaches.