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The Distribution of New Enhancing Lesion Counts in Multiple Sclerosis: Further Explorations

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ABSTRACT

Background: A statistical distribution describing the number of new enhancing lesions seen on MRI in patients with MS is of great importance for improving the statistical methodology of clinical trials using new enhancing lesions as outcome measure. We examined whether there are superior alternatives for the currently proposed negative binomial (NB) distribution.

Objective: To determine the optimal statistical distribution describing new enhancing lesion counts from a selection of six conceivable models, and to assess the effect on the distribution of a treatment effect, varying follow-up duration and selection for activity at baseline.

Methods: The statistical NB, Poisson-Inverse Gaussian (P-IG), Poisson-Lognormal (P-LN), Neyman type A (NtA), Pólya-Aeppli (PA) and Zero Inflated Poisson (ZIP) distribution were fitted on new enhancing lesion data derived from one treated and two untreated cohorts of RRMS and relapsing SPMS patients and on subgroups of varying follow-up duration and selection for baseline activity. Measure of comparison for the fit of the distributions was Akaike's information criterion.

Results: Both the subgroup analyses as well as a treatment had a noticeable effect on the distributional characteristics of new enhancing lesion counts. The NB distribution generally provided the most optimal fit, closely followed by the P-IG distribution and the P-LN distribution. Fits of the PA and NtA distribution were suboptimal, while the ZIP distribution was the least adequate for modelling new enhancing lesion counts.

Conclusion*:* The NB distribution is the optimal distribution for modelling new enhancing lesion counts, irrespective of the effect of treatment, follow-up duration or a baseline activity selection criterion.

INTRODUCTION

Gadolinium (Gd) enhanced magnetic resonance imaging (MRI) has become a valuable tool for monitoring the evolution of multiple sclerosis (MS). Gd-enhancing lesions represent areas of blood brain barrier disruption and inflammation, and serve as a measure of disease activity. At present, the number of new Gd-enhancing lesions is a widely used MRI outcome parameter in MS clinical trials.

Since we entered an era of altered ethical and practical considerations brought about by the availability of multiple approved agents for the disease, it is becoming increasingly more difficult to perform large placebo-controlled clinical trials. As such, the need for more efficient trial design and more accurate statistical assessment is increasing. An important step in optimizing future trials using the number of new enhancing lesions as an outcome parameter is describing the distribution of such lesions with an appropriate statistical model. Optimizing this model would not only allow for the use of more powerful methods in the assessment of treatment effects, but would also improve the accuracy of prospective sample size estimations by means of parametric simulation procedures.

The first statistical model proposed for describing the distribution of new enhancing lesion counts across patients over a fixed time period was presented by Sormani *et al* [1]. It was shown that the negative binomial (NB) model, a member of the distributional family of Poisson mixture models, gave an acceptable fit of new enhancing lesion data obtained from a cohort consisting of both relapsing remitting (RR) and secondary progressive (SP) MS patients. In a subsequent study [2], a comparable result with the NB model was found in a cohort of RRMS patients not selected for baseline activity, while the Poisson Inverse Gaussian (P-IG) distribution, a Poisson mixture model closely related to the NB model, gave a better fit for RRMS patients selected for activity at baseline. Although the fits in these studies are adequate, it is not ruled out that alternative distributions may prove superior in fitting new enhancing lesion data. Furthermore, all previous studies were performed on data derived from untreated patients, whereas the distribution of new enhancing lesion counts for a cohort undergoing treatment may deviate.

The objectives of this study are twofold. First, we aim to deduce the optimal distribution for describing new enhancing lesion counts in three available datasets from a selection of conceivable statistical models, by using Akaike's information criterion (AIC) as measure of comparison for the fit of the distributions on the

available data. Second, to assess the effect of treatment, duration of follow-up and selection for baseline activity on the distribution of new enhancing lesion counts, by fitting the statistical models on data derived from treated and untreated patients, and performing subgroup analyses based on varying follow-up duration and selection for the presence or absence of enhancement at baseline.

MATERIALS AND METHODS

New enhancing lesion data from three datasets were at our disposal. Patients underwent a baseline MRI scan, followed by either six (dataset A) or nine (dataset B and C) subsequent monthly MRI scans. All scan were performed in accordance with published guidelines for the use of MRI in clinical trials [3]. Patients were only included in the analysis if all six or nine observations were present.

Dataset A

This group consists of 169 RRMS patients who received varying doses of interferon beta-1a (IFNB-1a) or placebo orally every other day for six months. The cohort can be regarded as a natural history cohort as no clinical or MRI effect of any dose of IFNB-1a was observed [4]. It consists of 46 men and 123 women, with a mean age of 35.4 years (SD 8.4, range 18-58), a mean disease duration of 6.4 years (SD 5.3, range 1-28) and a median baseline expanded disability status scale (EDSS) of 2.0 (IQR 1.5-3.5). Patients were included when there were at least two clearly documented relapses within 24 months prior to study entry in conjunction with seven T2 lesions on the screening scan, or at least one clearly documented relapse within 24 months prior to study entry in conjunction with at least one Gd-enhancing lesion, and at least another three T2 lesions on the screening MRI.

Dataset B

This dataset is the placebo arm of the double-blind-placebo controlled multicentre oral temsirolimus trial [5], and consists of 69 patients with either RRMS or SPMS with superimposed relapses (57 and 12 respectively). There were 50 women and 19 men with a mean age of 38.5 years (SD 9.1, range 19-55), a mean disease duration of 5.9 years (SD 5.9, range 0–23) and a median baseline EDSS score of 2.5 (IQR 1.5-3.5). Patients were included if there was at least one documented relapse in the preceding

12 months before screening, or at least one documented relapse in the preceding 24 months before screening in conjunction with at least one Gd-enhancing lesion on the screening or baseline scan.

Dataset C

This dataset is the treatment arm of the same oral temsirolimus trial [5]. Patients were treated with 8 mg temsirolimus orally every day, and showed a 47.8% reduction in the number of new enhancing lesions compared with placebo.(p=0.01), an effect well within the range of comparable treatments in MS (29%- 87.5%) [6,7]. It consists of 76 patients (66 RRMS and 10 SPMS with relapses) with 49 women and 27 men, a mean age of 38.5 years (SD 8.4, range 20-57), a mean disease duration of 6.0 years (SD 5.2, range 0-24) and a median baseline EDSS score of 2.5 (IQR 1.5-4.0). Inclusion criteria were the same as for dataset B.

Statistical models

Six statistical models are analyzed in this study [8]. From the distributional family of Poisson mixture models, the NB distribution and P-IG distribution are included, together with the Poisson Lognormal (P-LN) distribution. Poisson mixture models are an extension of the basic Poisson distribution by replacing the fixed parameter mean with a random mean described by a second statistical model. In the NB model the mean of the Poisson distribution is described by the gamma distribution; the combination of the Poisson distribution with the Inverse Gaussian distribution creates the P-IG distribution and in the P-LN distribution, the mean follows a Lognormal distribution. When applied to lesion count data, a Poisson mixture model thus results in a variable mean expected number of lesions per patient instead of a fixed mean expected number, which in theory fits in more closely with the heterogeneous nature of MS.

A second distributional family derived from the Poisson distribution is the group of “compound Poisson distributions”, from which the Neyman-type A (NtA) distribution and the Pólya-Aeppli (PA) distribution are included. A compound Poisson distribution assumes that the expected count is the sum of *N* independent and identically distributed variables, where *N* is Poisson distributed. For new enhancing lesion counts this is conceivable as patients having a variable number of *N* “episodes” according to the Poisson distribution, with each episode generating a number of lesions described by an additional distribution. For the NtA distribution, the expected

number of new enhancing lesions is the sum of *N* Poisson distributed variables (with *N* being Poisson distributed) while in the PA distribution, the expected number of new enhancing lesions is the sum of *N* geometrically distributed variables (with *N* being Poisson distributed).

Lastly, the zero inflated Poisson distribution (ZIP) is included. This distribution consists of two components; one for producing counts that can only be zero, and one for producing the remaining counts which will follow a Poisson distribution. It is applied in data with an "excess" of zeros, a familiar scenario in cohorts of relapsing MS patients.

All distributions are chosen from a pragmatic point of view. Therefore, all the applied models are characterized by two parameters (Except the Poisson distribution, which is characterized by one parameter) and generally applicable in practice.

Furthermore, the NB, P-IG, NtA and PA distribution are two parameter count distributions that are "partially closed under addition" [9] and satisfy the property that the maximum likelihood estimator of the (population) mean equals the sample mean, both of which are convenient mathematical properties.

Statistical analysis

The fit of the applied statistical distributions was assessed by comparing the AIC as measure of the fit of the data for each distribution. In the AIC, the maximized log-likelihood value, a basic measure for the fit of a distribution on a given dataset, is adjusted for the number of parameters of the fitted distribution by: AIC = -2 (maximized log likelihood − # parameters in the model). In this way, a statistical model is penalized for the number of parameters. For comparison, the fit of the basic Poisson distribution was also included. The estimates were obtained with the statistical software packages: Stata version 10, StataCorp LP USA (Poisson, NB, P-LN, ZIP), MATLAB version R2007a, The MathWorks USA (P-IG, based on the procedure described by Karlis et al [10]) and GenStat version 9, VSNi United Kingdom (PA, NtA).

All fits were performed on the complete datasets (6 months follow-up for dataset A and 9 months follow-up for dataset B and C) as well as on the subsets of shorter follow-up duration (3 months for dataset A and 5 months for dataset B and C), selection for activity at baseline (defined by the presence of at least one Gd-enhancing lesion on the baseline scan) and selection for inactivity at baseline (defined by the absence of a Gd-enhancing lesion at the baseline scan (applied for dataset A, B and C).

RESULTS

Descriptive results are shown in Table 1. The percentages of inactive scans and inactive patients are lowest for dataset A. In line with the positive treatment effect, dataset C has the lowest number of new Gd-enhancing lesions per scan (0.77 lesions/scan) compared with dataset A (1.8 lesions/scan) and dataset B (1.2 lesions/scan). As expected, selection for the presence of an enhancing lesion at baseline resulted in more active subgroups, with less inactive scans and a higher mean number of new enhancing lesions.

The fits of the six analyzed statistical models and the Poisson distribution are presented as AIC values in Table 2 (best fitting model highlighted in bold). An AIC closer to zero signifies a superior fit, and values are only comparable within a dataset or subset. In general, the optimal fits for all three datasets are obtained with members of the distributional family of Poisson mixture models from which the NB distribution is the best fitting distribution in dataset A and C and dataset B is optimally fitted by the P-LN distribution, although the difference with the AIC of the NB is small.

In the subgroup analyses, a shorter follow-up duration has no effect on the shape of the distribution in dataset A and C since the optimal fitting model remains the NB distribution. Whereas the complete dataset B is fitted most optimally by the P-LN distribution and the shorter follow-up dataset B by the P-IG distribution, the differences with the NB distribution in both cases are again small. In the baseline activity subgroups, all groups are consequently fitted differently by one of the Poisson mixture models, preventing the assignment of a single distribution for matching a particular subgroup.

Finally the effect of treatment, as assessed by comparing dataset C with dataset A and B, has little influence on the goodness of fit since the datasets are NB-distributed (dataset A and C) or marginally deviating from the NB distribution (dataset B).

Table 3 summarizes the parameter estimates of the NB distribution. Particularly interesting is the effect of treatment on the NB-parameter theta. Except for the baseline activity subgroup, this parameter in constantly estimated in a range of 0.4–0.6, irrespective of the presence of treatment. These results suggest that the use of a constant theta-parameter in previous parametric sample size estimations based on the NB distribution [2] is valid.

Table 1 | Descriptive statistics of dataset A, B, C and subsets: % of inactive scans (proportion of scans with 0 new enhancing lesions), % of inactive patients (proportion of patients with 0 cumulative new enhancing lesions) and mean, median, SD and range of cumulative number of new enhancing lesions.

Data-set	Subgroup	Duration from BL (months)	n	Inactive Scans (%)	Inactive Patients (%)	New Enhancing Lesions			
						Mean	Median	SD	Range
A	Complete dataset	6	158	46.9	15.8	11.0	5.0	14.1	0-69
	short follow-up	3	166	48.0	27.1	5.7	2.0	8.6	0-50
	inactive at baseline	6	65	73.8	33.8	2.9	1.0	5.1	0-35
	active at baseline	6	93	28.1	3.2	16.6	12.0	15.7	0-69
B	Complete dataset	9	61	64.7	24.6	10.5	4.0	20.4	0-95
	short follow-up	5	65	64.9	32.3	5.4	2.0	11.6	0-70
	inactive at baseline	9	43	74.4	32.6	4.8	2.0	9.3	0-57
	active at baseline	9	18	41.4	5.6	24.1	9.0	31.4	0-95
C	Complete dataset	9	59	71.9	27.1	6.9	1.4	11.3	0-55
	short follow-up	5	64	63.1	31.3	5.7	1.2	9.7	0-54
	inactive at baseline	9	26	88.9	50.0	1.4	0.5	2.4	0-10
	active at baseline	9	33	58.6	1.0	11.2	2.4	13.5	0-55

Table 2 | AIC values of the fit of the Neyman-type A (NtA), Pólya-Aeppli (PA), negative binomial (NB) , Poisson Inverse Gaussian (P-IG), Poisson Lognormal (P-LN) Zero inflated Poisson (ZIP) and Poisson distribution on the complete dataset A, B, C and their subgroup analyses of shorter follow-up duration, selection for inactivity at baseline and selection for activity at baseline. Best fitting distribution marked in bold.

Dataset A

Subgroup Duration from Baseline*		Complete dataset (n=158) 6	Short follow up (n=166) 3	Inactive at baseline (n=65) 6	Active at baseline (n=93) 6
Distribution	NtA	1234.55	1031.31	308.95	774.72
	PA	1094.94	931.96	292.63	725.08
	NB	**1070.81**	**909.44**	286.20	**716.91**
	P-IG	1087.15	918.28	284.46	723.99
	P-LN	1102.98	919.39	**281.34**	719.46
	ZIP	2413.30	1599.13	399.27	1545.61
	Poisson	2871.60	2004.74	471.75	1620.35

* in months

Dataset B

Subgroup Duration from Baseline*		Complete dataset (n=61) 6	Short follow up (n=65) 3	Inactive at baseline (n=43) 6	Active at baseline (n=18) 6
Distribution	NtA	601.32	422.07	254.00	194.90
	PA	410.96	357.54	228.43	159.91
	NB	388.93	337.65	**222.57**	153.44
	P-IG	389.14	**332.07**	224.64	153.34
	P-LN	**385.57**	376.25	225.29	**144.21**
	ZIP	1261.89	785.75	398.42	612.67
	Poisson	1554.54	978.69	506.49	654.45

* in months

Dataset C

Subgroup		Complete dataset (n=59)	Short follow up (n=64)	Inactive at baseline (n=26)	Active at baseline (n=33)
Duration from Baseline*		6	3	6	6
Distribution	NtA	401.11	398.02	90.54	258.59
	PA	352.05	355.63	88.29	237.12
	NB	**340.70**	**346.13**	**87.51**	231.77
	P-IG	343.23	349.42	87.71	231.76
	P-LN	333.94	347.92	87.90	**231.72**
	ZIP	711.86	654.01	97.36	497.02
	Poisson	900.40	847.31	114.33	547.45

* in months

Table 3 | Parameter estimates of the negative binomial (NB) distribution in complete dataset A, B, C and subsets.

Dataset		NB-parameters*	
		μ	Θ
A	complete dataset	10.95	0.60
	Short follow-up	5.71	0.50
	inactive at baseline	2.88	0.57
	active at baseline	16.60	1.18
B	complete dataset	10.48	0.39
	short follow-up	5.42	0.37
	inactive at baseline	4.79	0.44
	active at baseline	24.06	0.67
C	Complete dataset	6.90	0.44
	Short follow-up	5.69	0.42
	inactive at baseline	1.42	0.51
	active at baseline	11.21	0.82

* μ = mean, $1/\Theta$ = dispersion, ie. var*iance* = $\mu + \mu^2/\Theta$.

Both the PA distribution and the NtA distribution are not superior to any of the two best fitting Poisson mixture models. As displayed in Figure 1 and Figure 2, the steady but rapid decline in the expected number of lesion counts as predicted by Poisson mixture models describes the skewed new enhancing lesion count data more accurately then the more abrupt course of the compound Poisson distributions. Furthermore it is notable that the NtA distribution adopts a multimodal shape, not fitting in with the empirical data. Lastly, the fits of the ZIP distribution gave the least promising results (no graphic shown).

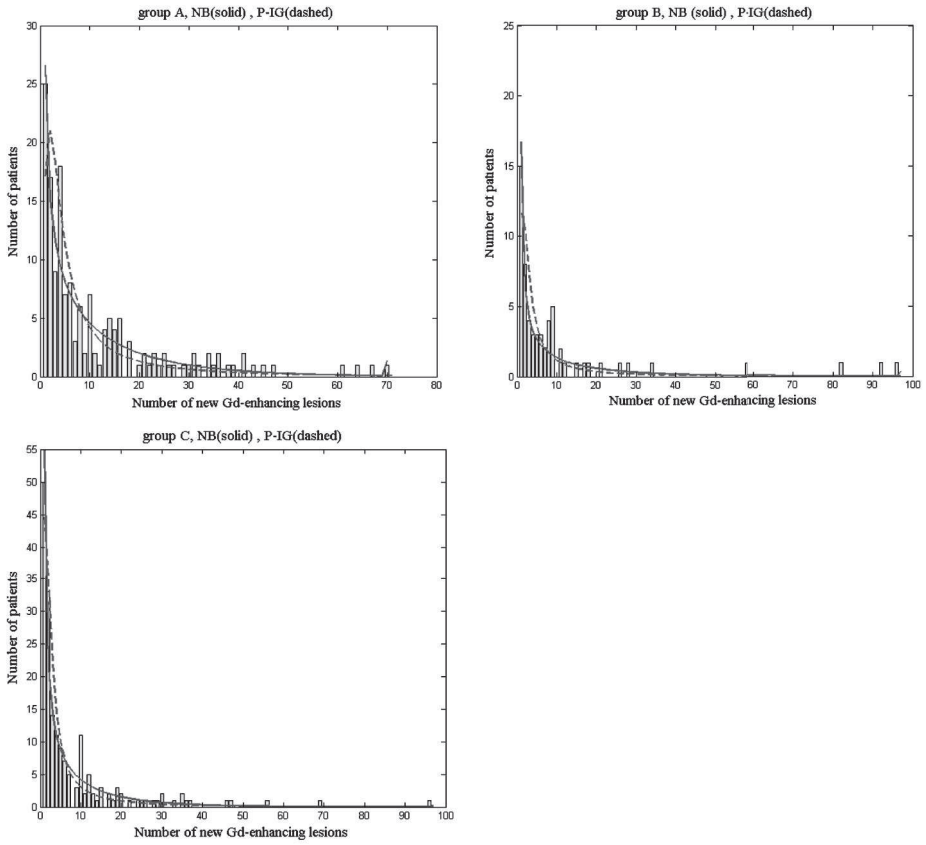

Figure 1 | Number of new Gd-enhancing lesions as observed (bars) and estimated by the negative binomial (NB) distribution (solid) and Poisson Inverse-Gaussian (P-IG) distribution (dashed) in the complete datasets A, B and C *(see page 156 for colour figure)*.

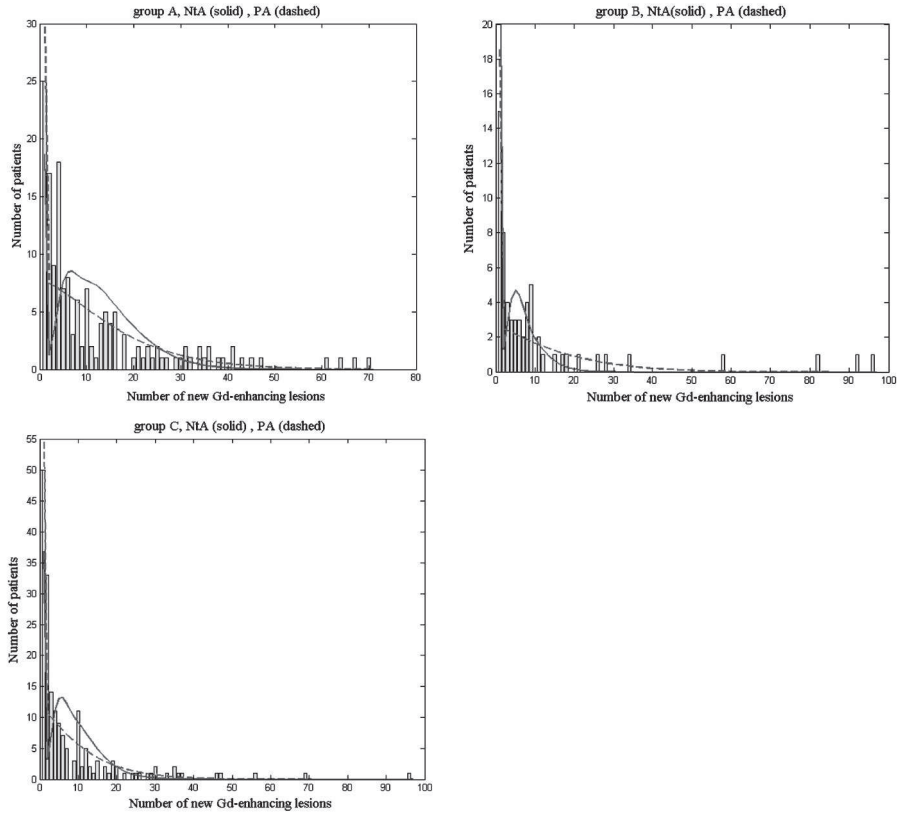

Figure 2 | Number of new Gd-enhancing lesions as observed (bars) and estimated by the Neyman type A (NtA) distribution (solid) and Pólya-Aeppli (PA) distribution (dashed) in the complete datasets A, B and C.

DISCUSSION

The number of new enhancing lesions is an MRI outcome measure known to vary greatly between patients. Its distribution is skewed, with the bulk of frequencies in the first five categories of counts and the value zero being most frequent. From the six statistical models analyzed in this study, all accounting to various extents for the above distributional characteristics, we found that the optimal and most constant distribution for modelling new enhancing lesion counts in relapsing MS patients is the NB distribution. Moreover, we showed that this optimal fit was practically unaffected

by the presence of a treatment effect, varying follow-up duration and selection for baseline activity.

The applied scenarios in which the distribution of new enhancing lesion counts was assessed in this study vary considerably in cohorts of MS treatment trials. As a result, the frequencies of new enhancing lesion counts are influenced and consequently, its distribution; when a cohort is selected for activity at baseline for example, this will result in an increase of patients with a higher number of accumulated new enhancing lesions, and a decrease of patients with zero or a single enhancing lesion. Conversely, treatment with an immunomodulatory drug should result in less enhancing lesions. Although the influence of all scenarios is clearly observed in the presented data (shown by the altered distributional characteristics for the treated cohort C and the subgroup analyses of all datasets: table 1) the NB distribution remained the optimal fitting model, suggesting that the NB distribution is a robust distribution, capable of adapting its shape to various distributional changes.

Another possible explanation for the steady fit of the NB distribution is that, irrespective of the subgroup drawn from the population, the fundamental shape of the distribution of new enhancing lesions remains NB. Thus, although the analyzed subgroups alter the distributional characteristics of the data, it merely causes a shift of the existing NB distribution, rather than a genuine distributional change.

The P-IG and P-LN distribution proved an adequate alternative for the NB distribution. The P-IG distribution has previously been applied for modelling new enhancing lesion counts, and was found to be superior to the NB distribution in data from cohorts selected for baseline activity [2]. Although our findings could not support this proposition, the results are to be interpreted with caution due to small sample sizes of the subgroups in dataset B and C. New in our analyses was the application of the P-LN distribution. Applied in various fields of research [11] it was chosen for its close resemblance to the NB model and the general availability of the lognormal distribution in statistical packages (A Poisson regression model with a log-link and a normal distributed random intercept results in the P-LN distribution). The fit of the P-IG distribution and the P-LN distribution outperformed the fit of the NB distribution on some occasions, but the differences were mostly small. In general, the relatively small differences in fit between the Poisson mixture models is a noticeable finding, and shows that the NB is not materially worse than its conceivable alternatives. We argue that the NB distribution is the overall optimal fitting model, not only because of the results in this study, but also because it is the most parsimonious distribution

of the distributions analyzed; It is considered a probability distribution per se and possesses convenient mathematical properties.

The PA and NtA distribution, frequently applied in entomological and ecological studies and a known alternative for the NB distribution [12], proved less promising in fitting new enhancing lesion data. In practice, the models showed an erroneous fit of the first five categories of counts, together with an abrupt change in the transition to the subsequent categories. Especially the NtA distribution, which has the characteristic that it can be multimodal [13], showed a marked deviation from the empirical data. While a mathematical explanation for our findings is complicated and out of scope for this exploratory study, the results show that new enhancing lesions are less clustered in periods over time than both compound Poisson distributions anticipated.

The final and least applicable distribution for modelling new enhancing lesion counts was the ZIP distribution. Its fit was a clear improvement compared to the Poisson distribution due to the increase in estimated zeros, but compared to the Poisson mixture models the zero category was still systematically underestimated. Therefore, the ZIP distribution is clearly the least feasible alternative.

Having large datasets at one's disposal is of particular importance when fitting statistical distributions. Although this explorative study does not quantify the potential sampling errors made for the differences in fit between the distributions, a bootstrap confidence interval [14] for the difference in AIC between the fit of the NB distribution and the P-IG distribution on the complete dataset A, (95%CI = [-0.92-33.56]) illustrates that an exact differentiation between the rivalling distribution is not yet achieved with the present data (the interval contains the null hypothesis). For drawing exact conclusions regarding the optimal two-parameter distribution describing new enhancing lesion counts therefore, multiple and preferably large datasets are required. Larger datasets are especially of interest, when future data modelling studies in MS advance to more complex, but potentially more accurately fitting statistical distributions such as three-parameter distributions or longitudinal hidden Markov models [15].

In conclusion, based on three independent datasets, our study strengthens the choice for the NB distribution as the overall optimal fitting model for describing the distribution of new enhancing lesion counts. For future designing and analysing MS clinical trials using the number of new enhancing lesions as outcome measure, this is an important confirmation of the valid application of statistical methodology based on the NB distribution.

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