Report

Signal detection of spontaneous medical device reports over time accounting for multiple comparisons

Ty Stanford, Lan Kelly, Marianne Gillam, et al.

Table of contents

[1. Abstract 2](#_Toc154170397)

[2. Introduction 3](#_Toc154170398)

[3. Methods 5](#_Toc154170399)

[3.1 Data aquisition 5](#_Toc154170400)

[3.2 Analysis data 9](#_Toc154170401)

[3.3 Signal detection over time 9](#_Toc154170402)

[3.3.1 Proportional reporting ratio (PRR) 10](#_Toc154170403)

[3.3.2 Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC) 11](#_Toc154170404)

[3.3.3 maxSPRT 11](#_Toc154170405)

[3.4 Analysis choices 13](#_Toc154170406)

[3.5 Software and code availability 13](#_Toc154170407)

[4. Results 14](#_Toc154170408)

[5. Conclusion 19](#_Toc154170409)

[6. Session information 20](#_Toc154170410)

<https://academic.oup.com/jamia/pages/General_Instructions>

**Research and Applications**

Research and Applications articles describe original work in the formulation, implementation, or evaluation of informatics-based studies and investigations. The articles do not need to be limited to hypothesis-driven research, and they can, for example, report on an innovative application of information technology, the detailed description of a new methodology, or the formulation and formative evaluation of a new model. The structured abstract should contain the headings: Objective, Materials and Methods, Results, Discussion, and Conclusion. The main text should, in addition to the sections corresponding to these headings, include a section describing Background and Significance.

(Word count: up to 4000 words. Structured abstract: up to 250 words. Tables: up to 4. Figures: up to 6. References: unlimited.)

**Brief Communications**

Brief Communications are short versions of Research and Applications articles, often describing focused approaches to solve a particular problem, or preliminary evaluation of a novel system or methodology.

Word count: up to 2000 words. Structured abstract: up to 150 words. Tables: up to 2. Figures: up to 3. References: unlimited.

# 1. Abstract

Objective

Materials and Methods

Results

Discussion

Conclusion

# 2. Introduction

Adverse events from implantable medical devices are commonly reported to regulatory bodies in the form of unstructured free-text in spontaneous reports. Detecting safety signals from the reports for post-market surveillance can be challenging. Spontaneous reports of adverse events may be submitted by manufacturers, clinicians and consumers to the Database of Adverse Event Notifications (DAEN), maintained by the Australian Therapeutic Goods Administration (TGA) in the form of unstructured free text. Pelvic (urogynaecological) mesh was used to treat women for pelvic organ prolapse and stress urinary incontinence. While the device provided benefits to some women, others experienced serious complications.

The pelvic mesh was removed from market in …

There is still ongoing heath, financial and legal fallout from the device’s use [Dec 22](https://www.abc.net.au/news/2022-12-04/mesh-implant-class-action-shine-lawyers-payout-dispute/101728850)

Post-market safety signal detection plays an important role in ongoing monitoring of medical devices and medicines at large scales. The oft-considered gold standard of clinical trials are normally targeted for effectiveness outcomes and do not have to the scope or data abundance to monitor multi-system safety signals. Large spontaneous report databases provide large-scale data, whether nationally or internationally, that can be mined to uncover disproportionate numbers of adverse events reported based on exposure groups (medical device classifications for example). Uncovered relationships of disproportionate adverse event reporting may be used for screening of more targeted investigations of the exposure-outcome pairs for patient safety.

Oftentimes, signal detection is performed at snapshots in time based on specific concerns or interest in the exposure or outcome. A more complicated periodic re-assessment of safety signals is also possible. This can be done by alpha-adjustment of the to account for multiple looks at the estimates over time, or use methods like maxSPRT which also consider multiple looks at the potential signal estimates, however the detection thresholds are calculated so the type I error remains nominal for the entirety of the follow-up.

Considered here are the periodic signal detection methods as we aim to retrospectively determine, if periodic evaluation of safety signals (specifically for pain) were assessed for pelvic mesh, at what point would a signal have been detected.

Traditionally, signal detection mining has used structured data in spontaneous databases based on structured reports from patients, medical practitioners, government bodies or device or medication sponsors. However, with both the increase in digital data such as free-text data, maturing natural language processing machine learning methods and increased computational power, an opportunity is available to leverage free-text data in safety signal detection.

[has there been any NLP of free-text in adverse events/safety monitoring? Need to do literature search of examples + references]

The purpose of this study was to develop an end-to-end pipeline, utilising free-text information to screen for medical device safety issues, using an Australian spontaneous report database of medical device adverse events (Database of Adverse Event Notifications, DAEN). The study aims to evaluate the feasibility of disproportional reporting rate methods to detect signals in free-text descriptions of adverse events using natural language processing (NLP) to classify DAEN reports into topics by:

1. implementing over time, repeated look adjusted disproportional reporting rate (“signal detection”) algorithms on medical device adverse event data,
2. reporting retrospective time-to-signal findings for pelvic mesh devices associated with pain adverse events for analysis pipeline feasibility,
3. evaluating the sensitivity of signal detection methods to assumed data accumulation length and rates (e.g., the critical value calculation for maxSPRT), and
4. comparing the retrospective time-to-signal to the timings of the withdrawl of pelvic mesh devices in Australia.

# 3. Methods

The DAEN spontaneous database was searched for free-text reports on all medical devices from 2012-2017 with an eye to focus on mesh devices and pelvic mesh, specifically, reporting pain as a post surgery outcome. Topic modelling, a Natural Language Processing (NLP) technique, was used to profile the unstructured text into mixtures of clinically relevant topics. A report was considered to contain a particular topic if the probability it contains words relating to the topic, P(topic = | document), was over a certain threshold, therefore denoting a presumptive “pain” spontaneous event.

Disproportionality analysis was used to detect potential signals from the most frequent clinical topic from pelvic mesh, with hernia mesh and other devices used as comparators. Measures are based on a contingency table for the number of adverse events with and without the most frequent topic in the device of interest and the comparator.

Testing was performed on the DAEN at quarterly intervals, if new data were accumulated in the interval, over the study period, commencing in 2012.

## 3.1 Data aquisition

The data is thanks to [curtis-murray](https://github.com/curtis-murray) at his [MedicalDevicesNLP](https://github.com/curtis-murray/MedicalDevicesNLP) repo

* Natural language processing of the TGA spontaneous reports of medical device database (DAEN)
* Each record has an estimate of P(topic == "pain" | Level, Doc) using hierarchical stochastic block modelling (hSBM)
* P(topic == "pain" | Level, Doc) estimates for each record are roughly interpreted as the proportion of the NLP analysed free text that is considered as using/describing words related to pain

And example record and processing values (description limited to 150 characters):

| ReportID | Report date | Class | Device | P(‘pain’|doc) | ARTG no. | Event | Source | Event type | Description |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 37537 | 2015-02-06 | other\_device | Class IIa | 0.029 | 137859 | Injury | Industry | Mechanical | Patient admitted for routine SFA angioplasty. The physician had completed the procedure without incident and had withdrawn the balloon catheter fro… |
| 36797 | 2015-08-27 | other\_mesh | Class III | 0.020 | 219240 | Injury | Industry | Material | 3 weeks post-op, patient contacted the surgeon saying that the wound was opening, and she could see the implant. The patient sent photos, and there… |
| 40917 | 2016-04-24 | pelvic\_mesh | Class IIb | 0.538 | 92718 | Injury | Consumer | Other | Have had pelvic pain, pain with sex incontinence with bowel and bladder, cannot sit, walk, stand on feet for extended time. |
| 45432 | 2017-03-29 | hernia\_mesh | Class IIb | 0.214 | 98833 | Injury | Consumer | Other | Atrium mesh implanted in my abdomen. Severe right sided abdominal pain ongoing. Also had further surgery to repair hernia due to reoccurrence of he… |
| 44402 | 2017-12-01 | other\_device | Class III | 0.000 | 149128 | No Injury | Other | Other | Sponsor distributed a Customer Letter dated 20th December 2016 announcing the immediate discontinuation of their CE-marked Umbilical Vessel Cathete… |
| 45624 | 2017-12-04 | other\_device | Class 1 | 0.000 | 121950 | No Injury | Health Professional | Mechanical | Operating table started tilting patient on its own during procedure. Emergency stop button pressed - table stopped briefly and began to tilt patien… |
| 45265 | 2017-12-18 | other\_device | Class IIb | 0.250 | 177101 | Injury | Industry | Other | Pain, possible rupture and swelling around prosthesis. |

## 3.2 Analysis data

Signal detection of disproportionate adverse events (AEs) will often have tabulated count data accumulated over time. The data at time point can be summarised as below:

|  | AE(s) | AE(s) |
| --- | --- | --- |
| Target exposure |  |  |
| Comparator exposure |  |  |

where

* AE(s) is the set of AEs (or singular AE) of interest,
* AE(s) is the complementary set to the AEs of interest,
* *Target exposure* is the medical device(s) of interest,
* *Comparator exposure* is the medical devices to which the *Target exposure* is being compared, and
* , , and (all ) are the respective counts of AEs recorded up until (i.e., cumulative) time .

In the motivating example of the pelvic mesh device, the contingency table can be written more specifically as

|  | Pain AEs | Not pain AEs |
| --- | --- | --- |
| Pelvic mesh |  |  |
| Comparator exposure |  |  |

where

* *AEs pain* is the count of AEs that contain “pain” themes greater or equal to some pre-specified threshold as estimated by the hSBM (that is, ), and
* *Comparator exposure* can be any relevant set of medical devices to compare the pelvic mesh to (e.g., hernia mesh or all other mesh devices or all other devices).

## 3.3 Signal detection over time

We will consider the three signal detection statistics below:

* Proportional reporting ratio (PRR),
* Bayesian Confidence Propagation Neural Network Information Component (BCPNN IC with MCMC CIs), and
* the maxSPRT statistic

As signal detection is being undertaken repeatedly as data are being accumulated, alpha spending needs to be considered. The below table classifies the aforementioned signal detection methods by their null hypothesis as well as how they control for the family-wise error rate (FWER).

| Method | Null hypothesis | FWER adjustment |
| --- | --- | --- |
| PRR | Ratio of pain AEs to all AEs in target and comparator groups has a ratio of 1 | PRR with -spending scheme |
| BCPNN IC | Independence of pain AEs and target group (based on marginal counts) | IC with -spending scheme |
| maxSPRT (binary, group sequential) | Log-likelihood ratio test statistic below null derived threshold | (built in) |

We will demonstrate how the group sequential binary maxSPRT, as described in previous work, is equivalent to a natively FWER-controlled PRR method of signal detection using the log-likelihood ratio test for significance.

Methods used included the Bayesian Confidence Propagation Neural Network (BCPNN) and the maximised Sequential Probability Ratio Test (maxSPRT) which accounted for multiple testing through alpha spending. The BCPNN was used with and without adjusting for multiple testing. The test statistic for BCPNN is the information criterion (IC) which represents the log2 of the ratio of observed to expected adverse events (0 under the null hypothesis of no association between the topic and pelvic mesh).

maxSPRT was developed for near continuous sequential monitoring (called “group sequential” when monitored at discrete time points or after set accumulations of events), maintaining the correct overall alpha level. The test statistic is based on the maximized (log-)likelihood ratio statistic which uses the observed and expected (under the null hypothesis) reporting ratio assuming binomial adverse event accumulation. The critical value of the likelihood ratio statistic is determined by the 100(1-α)% quantile of possible likelihood ratio statistics from binomial adverse event counts under the null hypothesis over the entire group sequential follow-up.

### 3.3.1 Proportional reporting ratio (PRR)

The PRR estimate is calculated

In the context of signal detection, an elevated proportional reporting ratio is of concern. Therefore the one-sided hypothesis test (proportional reporting of the target is less than the comparator) is used and is not rejected until

at the level where is the quantile of the standard normal distribution. The above threshold is equivalent to the lower bound of the approximate % confidence interval for a standard two-sided hypothesis test.

### 3.3.2 Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC)

The Information Component (IC) statistic is an estimate of the observed-to-expected ratio of the number of target exposure AEs of interest on the log-scale under independence between the target exposure and AEs of interest based on information theory [(Bate et al., 1998)](https://doi.org/10.1007/s002280050466)

where denotes the marginal probability of an observed count for the target exposure, denotes the marginal probability of an observed count for the AE of interest, and denotes the joint probability.

The BCPNN IC of [Noren et al. (2006)](https://doi.org/10.1002/sim.2473) uses a Bayesian inference based *maximum a posteriori* (m.a.p.) central estimate of the IC,

where , and are the (assumed constant over time) underlying probabilities of the multinomial-distributed observed events , and , respectively ( corresponding to the count also included). The underlying probabilities are modelled using Dirichlet priors resulting in a Dirichlet posterior distribution. The one-sided null hypothesis of the joint probability target exposure and AEs of interest is equal or less than the marginal products () can be rejected when the quantile of the Markov Chain Monte Carlo (MCMC) empirical distribution is greater than 0. Similarly to the rejection rule for the PRR, this threshold corresponds to the lower bound of the % equal-tailed credible region in a two-sided hypothesis test.

### 3.3.3 maxSPRT

[Kulldorff et al. (2011)](https://doi.org/10.1080/07474946.2011.539924) outlined that the relative risk (RR) at a given point-in-time for accumulated binary data (that is, “success”/“failure” events or AE of interest or not) of a target group relative to a comparator has the maximum likelihood estimate of

where

* is the ratio of the total AEs for the comparator to the total AEs for the target,
* is the count of target exposure AEs in ,
* is the count of all AEs in (target and comparator exposure), and
* is therefore the count of comparator exposure AEs in .

In the context of our data, the values , and are the quantities , and , respectively, at time .

Therefore the RR maximum likelihood estimate at time can be re-written

which is the PRR estimate at time as before.

The (maximised) log-likelihood ratio statistic of (equivalently, ) can be determined calculated as

The maxSPRT test is considered significant when is greater than the pre-computed critical value which is the % percentile of the values generated under the null hypothesis for group sequential looks at the data . The CV can either be computed using the 95th percentile of values with the exact joint binomial probabilities over looks of the data accumulation under the null hypothesis, or by MCMC sampling of binomial event accumulation (and associated values) to approximate the distribution when the exact CV computation is computationally intractable.

## 3.4 Analysis choices

A large unknown what threshold should be used to dichotomise P(topic == "pain" | Doc) into pain and non-pain spontaneous event report. The threshold can roughly be interpreted as the proportion of the spontaneous event report free text relates to “pain” topics. It is a balancing act, likely with some “safe zone”, to choose a threshold high enough that false-positive pain reports don’t occur too frequently to induce noise or bias that might exist between the two device groups being compared, and also importantly a threshold low enough that pain events are not missed with false negatives and having the flow on effect of not having enough events of interest to sufficiently power the disproportionality statistics. From pilot feasibility exploration, the thresholds considered were from 0.5% to 10% of the free text, i.e., using thresholds . Further complicating matters, it should be noted, optimal P(topic == "pain" | Doc) thresholds may be different for differing event topics, however, we only consider the pain topic in this study.

We choose to perform the analysis group sequential analysis at quarterly time points as this is a reasonable accumulation of events in the Australian specific data source and represents a data accumulation interval feasible for large scale medical device safety monitoring given the computational and pipeline complexity of NLP of the free text and downstream analysis.

There are a vast amount of options in choosing an alpha-spending function to use with the BCPNN IC (lower) confidence interval calculations. However, we have chosen the widely used exponential spending function (Anderson and Clark, 2009) with because of its wide use and reasonable proporties.

The statistical analysis enumerates the following choices:

* comparator: pelvic mesh is compared to a range of specific (hernia mesh) to less specific (all other devices) comparator groups to characterise analysis performance,
* pain topic threshold, and
* competing signal detection methods in alpha-spend adjusted BCPNN IC calculations and maxSPRT.

## 3.5 Software and code availability

All analysis was performed in R (version X.Y.Z) with the assistance of the Sequential (ref) and EmpiricalCalibration (ref) packages for maxSPRT threshold calculation. All data and code is available at https://github.com/tystan/mesh-sig-detect.

# 4. Results

A summary depiction of the NLP processed data is shown in Figure 1. All spontaneous reports (n= ) were partitioned by device type as either pelvic mesh, hernia mesh, other mesh or other devices. Pelvic mesh had the highest proportion of reports that included the word “pain” in the free text, followed by other and hernia mesh. The stacked and stratified histograms in Figure 1 depict the NLP estimated P(pain|doc) distributions. Pelvic mesh had the largest proportion of non-0 estimated P(pain|doc) values when “pain” was used in the free-text. Notably, other mesh had a similar proportion of non-0 estimated P(pain|doc) values when “pain” wasn’t used in the free-text. It is worth remarking that these are the summary data at the conclusion of data follow-up in 2017 so the accumulation of data may not show such stark difference in pain adverse events (whether literal “pain” text or P(pain|doc) estimated) between the device categories.

|  |
| --- |
| Frequency of pain topic in pelvic, hernia and other mesh and other devices. |

To illustrate the quarterly accumulation of spontaneous report data, Table 5 is a snippet (each quarter up to 2015-Q1) of the cumulative number of pelvic mesh reports with and , labelled and respectively, as well as the cumulative number of hernia mesh reports with and , similarly labelled and . Each row of the table can be considered the cumulative contingency at time . It is notable the number of presumptive pain related adverse events in pelvic mesh spontaneous reports () increased sharply in Q4 2014 compared with the previous quarter. This pattern was consistent across the various thresholds considered in the analyses. [Include the reason this might be the case here].

Cumulative quarterly AE counts of pelvic mesh ( is pain topic count) compared to hernia mesh ( is pain topic count) using a pain topic threshold of 0.05.

| Quarter |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 2013-Q3 | 1 | 4 | 12 | 1 | 10 |
| 2013-Q4 | 2 | 6 | 14 | 1 | 10 |
| 2014-Q1 | 3 | 6 | 14 | 1 | 11 |
| 2014-Q2 | 4 | 7 | 15 | 1 | 14 |
| 2014-Q3 | 5 | 9 | 17 | 3 | 21 |
| 2014-Q4 | 6 | 26 | 19 | 4 | 27 |
| 2015-Q1 | 7 | 27 | 19 | 4 | 28 |
| 2015-Q2 | 8 | 27 | 19 | 4 | 28 |
| 2015-Q3 | 9 | 27 | 20 | 4 | 28 |
| 2015-Q4 | 10 | 27 | 20 | 6 | 28 |
| 2016-Q1 | 11 | 30 | 21 | 6 | 28 |
| 2016-Q2 | 12 | 34 | 21 | 6 | 28 |
| 2016-Q3 | 13 | 34 | 21 | 7 | 33 |
| 2016-Q4 | 14 | 36 | 23 | 7 | 33 |
| 2017-Q1 | 15 | 45 | 23 | 8 | 34 |
| 2017-Q2 | 16 | 58 | 24 | 8 | 37 |
| 2017-Q3 | 17 | 68 | 24 | 8 | 38 |
| 2017-Q4 | 18 | 77 | 25 | 8 | 38 |

While not the values used for determining significance, Figure 2 demonstrates the statistics, termed here as “reporting ratio statistics”, over the follow-up period that are most likely the familiar signal detection estimates to the reader. The specific comparison seen is for pelvic mesh (target) vs hernia mesh (comparator) for four different thresholds. The RR estimates for maxSPRT and PRR methods are of course identical, the methods differ in using the LRT and Wald tests respectively. The IC statistic is not directly comparable to RR, it does share similarities in that values above the null value of 0 (on the log2 scale) represent disproportionate reporting rate in the cohort of interest. Plotted however is as this is a ratio-scale statistic that can be more easily compared to a RR. Note these reporting ratio statistics are not affected by multiple comparison adjustment.

Vertical lines are when H0 is rejected for the various methods which don’t necessarily coincide with the largest reporting ratio estimate but with the testing procedure used. Significance was reached at the same time for all methods (last quarter of 2014), except for the PRR method at the 0.08 threshold which was a delayed an additional quarter. The jumps in the reporting ratios were larger for larger thresholds, however it should be noted higher thresholds stopped reporting ratios being estimated until further into the follow up because less spontaneous report free text records are classified as pain events as a result of elevated estimated probability criteria (threshold).

(include a 2^IC vs RR numeric example here to compare reporting ratios)

The columns of Figure 2 depict increasing pain topic thresholds. Within each threshold, the reporting ratio estimates are reasonably stable after some initial fluctuation as a result of the uncertainty discrete nature of the data accumulated over time. However, the RR estimates for the larger thresholds show a general increase in the reporting ratio estimates over time. Interestingly, this is not the case for the BCPNN which actually decreases for the 0.08 threshold from 2016 onward. Common to all methods though are increased reporting ratio estimates for larger thresholds within their respective method suggesting that larger P(topic = “pain”| document) are more frequent in the pelvic mesh group. This higher threshold comes with a cost, that the higher barrier to pain events means insufficient data are available to produce a reporting ratio estimate early in the data accumulation. Further demonstrating competing constraints of a threshold low enough to detect sufficient presumptive pain events but high enough (specific enough) to discriminate between non-pain and pain events.

|  |
| --- |
| Reporting ratio estimates for the pelvic mesh v hernia mesh comparison over time for the three signal detection methods at different pain topic thresholds. |

Figure 3 shows how significance is determined for the three methods over time and for various comparisons (a fixed is used). Similarly to Figure 2, the vertical lines shows when significance is reached. The CV values for each maxSPRT analysis for the different comparators are different (values here), although not obvious from the graph. Also note that the LLR values have been truncated when exceeding 30 to not dominate the y-axis scaling.

The Hernia mesh v Other mesh group in the final column servea a negative control as it is not expected to produce a significant signal. Indeed no signal detection method reaches significance for this comparison.

Significance is reached in all methods when hernia mesh is the target. However the comparisons hernia mesh vs pelvic mesh and hernia mesh vs pelvic/other mesh rejected the null hypothesis a year later than the hernia mesh vs pelvic/other mesh/other devices comparison. This may be a result of difference safety profiles for non-mesh devices in the comparator counts ( and ). Consideration needs to be made about whether this is an appropriate comparison. Discussed in other articles (refs).

Warning: Removed 54 rows containing missing values (`geom\_vline()`).

|  |
| --- |
| Disproportionality test statistic values for heneria mesh compared to three copmparison groups over time with their respective critical values. The P(topic = ‘pain’| document) threshold is set at 0.04. |

Warning: Removed 54 rows containing missing values (`geom\_vline()`).

Figure 4 shows how the different signal detection methods reached significance at different pain thresholds . The highest thresholds risk delayed signal detection or not reaching significance at all, especially in the least data rich comparison of pelvic mesh v hernia mesh.

xxx where the thresholds that ensured all methods for the mesh only comparisons were detected prior to 2015

while the PRR allowed earlier potential signal detection in the pelvic mesh vs pelvic/other mesh/other devices comparison (2012 Q4) for thresholds xxxx, these thresholds were sub-optimal for the other methods of signal detection

|  |
| --- |
| Time when methods reached critical values for signal detection. |

Figure 5 explores the information about follow-up that is only available retrospectively that may affect signal detection if not approciximately estimated ahead of time. maxSPRT requires both the expected ratio of controls to cases ( to in this case) as data is accumulated as well as the expected number of reports per quarter (for a finite follow up period). Figure 5 shows how the time-to signal is alterd with changing assumed values that affect the CV thresholds for significance.

|  |
| --- |
| Time when methods reached critical values for signal detection using different assumed a priori variables for CV calculation. |

# 5. Conclusion

Urogynaecological mesh was withdrawn from the Australian market in 2018, while our retrospective analysis with a 0.06 threshold detected signals between August – December 2014. We have demonstrated the potential of using topic modelling in spontaneous reports for signal detection in post-market surveillance.

# 6. Session information

format(Sys.time(), '%d %b %Y')

[1] "22 Dec 2023"

sessionInfo()

R version 4.3.1 (2023-06-16 ucrt)  
Platform: x86\_64-w64-mingw32/x64 (64-bit)  
Running under: Windows 10 x64 (build 19045)  
  
Matrix products: default  
  
  
locale:  
[1] LC\_COLLATE=English\_Australia.utf8 LC\_CTYPE=English\_Australia.utf8   
[3] LC\_MONETARY=English\_Australia.utf8 LC\_NUMERIC=C   
[5] LC\_TIME=English\_Australia.utf8   
  
time zone: Australia/Adelaide  
tzcode source: internal  
  
attached base packages:  
[1] stats graphics grDevices utils datasets methods base   
  
other attached packages:  
 [1] arrow\_12.0.1.1 gsDesign\_3.5.0 knitr\_1.43 ggrepel\_0.9.3   
 [5] ggthemes\_5.0.0 ggplot2\_3.4.2 stringr\_1.5.0 lubridate\_1.9.2  
 [9] forcats\_1.0.0 tidyr\_1.3.0 dplyr\_1.1.2 readr\_2.1.4   
  
loaded via a namespace (and not attached):  
 [1] gt\_0.9.0 utf8\_1.2.3 generics\_0.1.3 xml2\_1.3.5   
 [5] stringi\_1.7.12 hms\_1.1.3 digest\_0.6.33 magrittr\_2.0.3   
 [9] evaluate\_0.21 grid\_4.3.1 timechange\_0.2.0 fastmap\_1.1.1   
[13] jsonlite\_1.8.7 purrr\_1.0.1 fansi\_1.0.4 scales\_1.2.1   
[17] textshaping\_0.3.6 cli\_3.6.1 rlang\_1.1.1 bit64\_4.0.5   
[21] munsell\_0.5.0 withr\_2.5.0 yaml\_2.3.7 tools\_4.3.1   
[25] tzdb\_0.4.0 colorspace\_2.1-0 assertthat\_0.2.1 vctrs\_0.6.3   
[29] R6\_2.5.1 lifecycle\_1.0.3 bit\_4.0.5 ragg\_1.2.5   
[33] pkgconfig\_2.0.3 pillar\_1.9.0 gtable\_0.3.3 glue\_1.6.2   
[37] Rcpp\_1.0.11 systemfonts\_1.0.4 xfun\_0.39 tibble\_3.2.1   
[41] tidyselect\_1.2.0 rstudioapi\_0.15.0 farver\_2.1.1 xtable\_1.8-4   
[45] htmltools\_0.5.5 labeling\_0.4.2 rmarkdown\_2.23 compiler\_4.3.1