

016 - Inference about a Population Rate (λ)

EPIB 607 - FALL 2020

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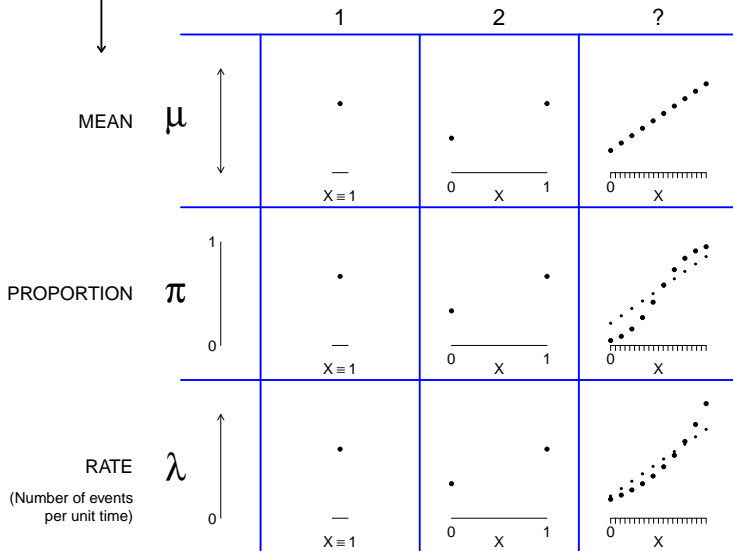
slides compiled on October 28, 2020



Parameter
Genre



Number of Parameters



Motivating example: HPV-16 Vaccine

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A CONTROLLED TRIAL OF A HUMAN PAPILLOMAVIRUS TYPE 16 VACCINE

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FOR THE PROOF OF PRINCIPLE STUDY INVESTIGATORS

Motivating example: HPV-16 Vaccine

- **Background:** $\approx 20\%$ of adults become infected with human papillomavirus type 16 (HPV-16), some of which progress to anogenital cancer.

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- **Methods:**
 - ▶ Randomly assigned 2392 young women (females age 16-23) to receive three doses of placebo or HPV-16 virus-like-particle vaccine (40 μg per dose), given at day 0, month 2, and month 6.
 - ▶ Genital samples to test for HPV-16 DNA were obtained at enrollment, one month after the third vaccination, and every six months thereafter.
 - ▶ The primary end point was persistent HPV-16 infection, defined as the detection of HPV-16 DNA in samples obtained at two or more visits.

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 - ▶ The primary end point was persistent HPV-16 infection, defined as the detection of HPV-16 DNA in samples obtained at two or more visits.
- **Results:**
 - ▶ Median follow-up time of 17.4 months
 - ▶ Incidence of persistent HPV-16 infection:
 - ▶ Placebo: 3.8 per 100 woman-years at risk
 - ▶ Vaccine: 0 per 100 woman-years at risk

Table 3

TABLE 3. EFFICACY ANALYSES OF A HUMAN PAPILLOMAVIRUS TYPE 16 (HPV-16) L1 VIRUS-LIKE-PARTICLE VACCINE.

TYPE OF ANALYSIS	END POINT	HPV-16 VACCINE				PLACEBO				OBSERVED EFFICACY (95% CI)*	P VALUE
		NO. OF WOMEN	CASES OF INFECTION	WOMAN-YR AT RISK	INFECTION RATE PER 100	NO. OF WOMEN	CASES OF INFECTION	WOMAN-YR AT RISK	INFECTION RATE PER 100		
					WOMAN-YR AT RISK %				WOMAN-YR AT RISK %		
Primary per-protocol efficacy analysis†	Persistent HPV-16 infection	768	0	1084.0	0	765	41	1076.9	3.8	100 (90–100)	<0.001
Efficacy analysis including women with general protocol violations‡	Persistent HPV-16 infection	800	0	1128.0	0	793	42	1109.7	3.8	100 (90–100)	—§
Secondary per-protocol efficacy analysis†	Transient or persistent HPV-16 infection	768	6	1084.0	0.6	765	68	1076.9	6.3	91.2 (80–97)	—§

Question: For Primary and Secondary per-protocol efficacy analysis, calculate a 95% CI of infection rate per 100 woman-years at risk for vaccine and placebo group.

Normal Approximation Based CI for the Count

Primary analysis:

```
# Vaccine group
qnorm(p = c(0.025, 0.975), mean = 0, sd = sqrt(0))

## [1] 0 0

# Placebo
qnorm(p = c(0.025, 0.975), mean = 41, sd = sqrt(41))

## [1] 28 54
```

Normal Approximation Based CI for the Count

Secondary analysis:

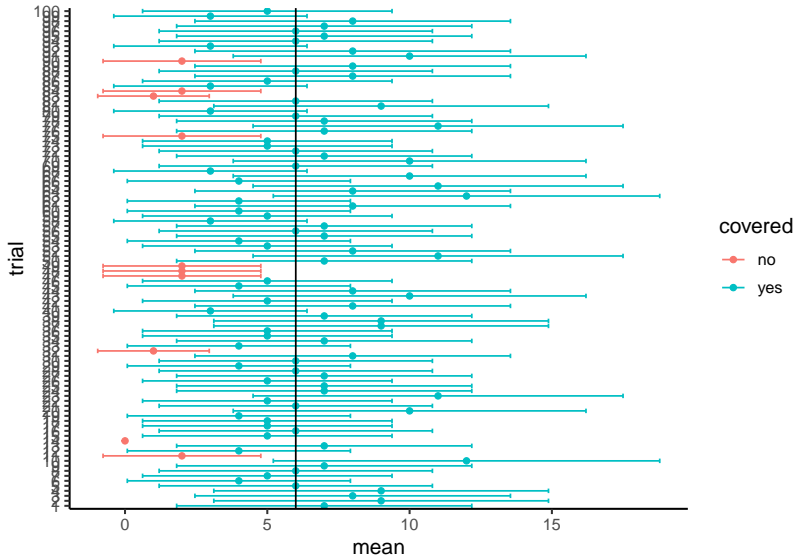
```
# Vaccine group
qnorm(p = c(0.025, 0.975), mean = 6, sd = sqrt(6))

## [1] 1.2 10.8

# Placebo
qnorm(p = c(0.025, 0.975), mean = 68, sd = sqrt(68))

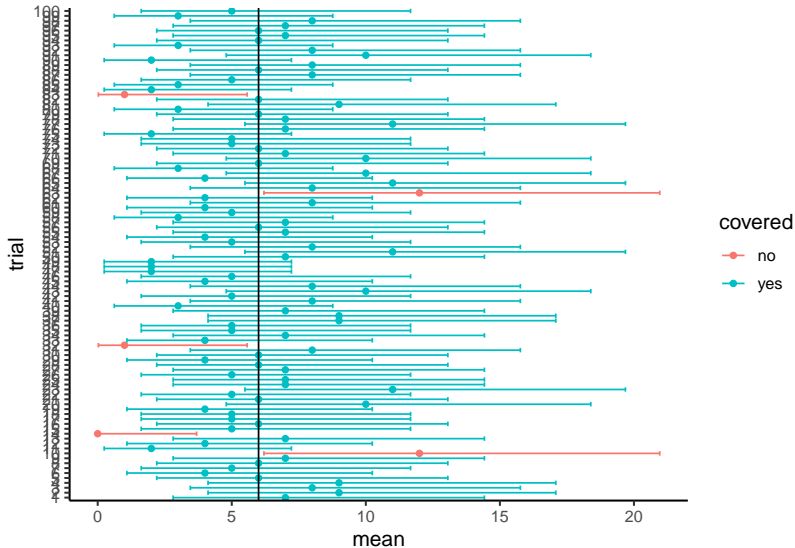
## [1] 52 84
```

Coverage Probability of Normal Approx. - Truth is $\text{Poisson}(\mu = 6)$



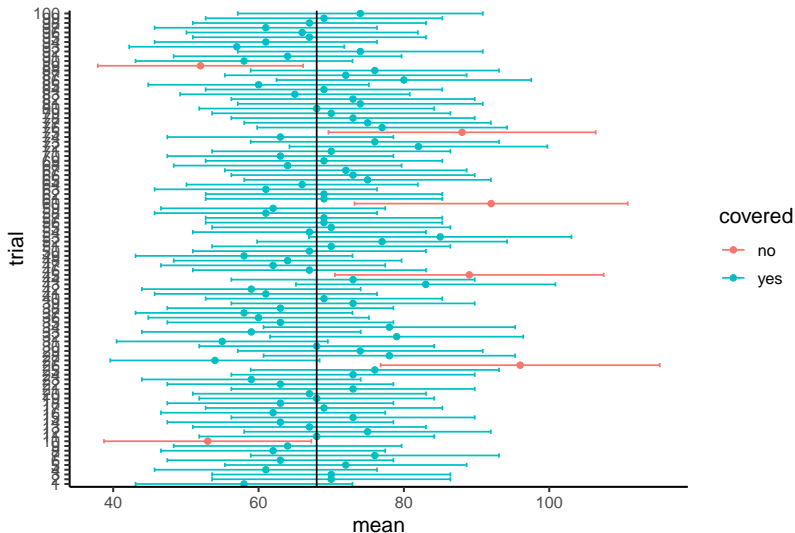
Each 95% CI was calculated using the Normal Approximation. Median CI width is 9.60

Coverage Probability of Exact Method - Truth is $\text{Poisson}(\mu = 6)$



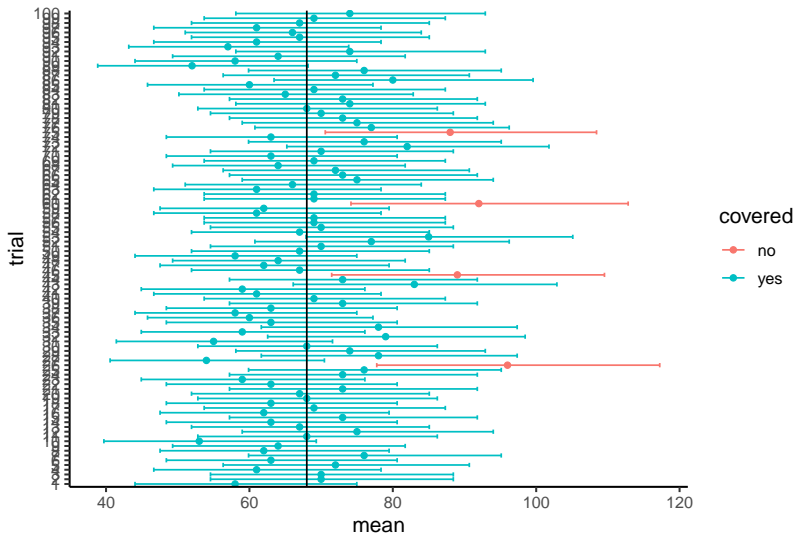
Each 95% CI was calculated using Poisson model. Median CI width is 10.86

Coverage Probability Normal Approx. - Truth is Poisson($\mu = 68$)



Each 95% CI was calculated using the Normal Approximation. Median CI width is 32.44

Coverage Probability Exact Method - Truth is $\text{Poisson}(\mu = 68)$



Each 95% CI was calculated using Poisson model. Median CI width is 33.52

The Poisson Distribution

- The (infinite number of) probabilities $P_0, P_1, \dots, P_y, \dots$, of observing $Y = 0, 1, 2, \dots, y, \dots$ events in a given amount of “experience.”
- These probabilities, $P(Y = k) \rightarrow \text{dpois}()$, are governed by a single parameter, the mean $E[Y] = \mu$ which represents the expected **number** of events in the amount of experience actually studied.
- We say that a random variable $Y \sim \text{Poisson}(\mu)$ distribution if

$$P(Y = k) = \frac{\mu^k}{k!} e^{-\mu}, \quad k = 0, 1, 2, \dots$$

The Poisson Distribution

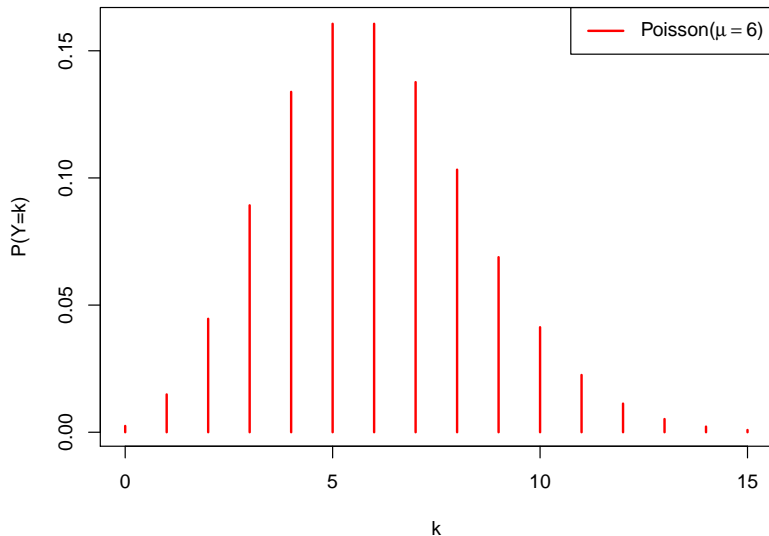
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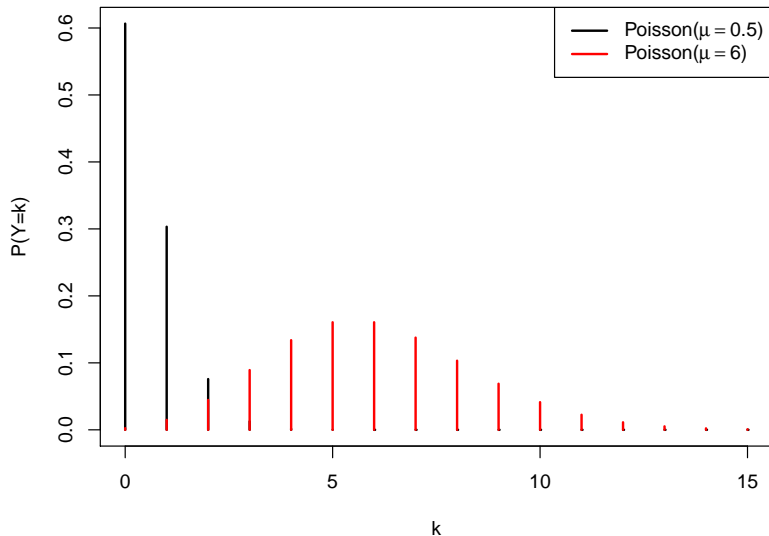
- Note: in `dpois()` μ is referred to as `lambda`
- Note the distinction between μ and λ
 - ▶ μ : expected **number** of events
 - ▶ λ : **rate** parameter

The probability mass function for $\mu = 6$

```
dpois(x = 0:15, lambda = 6)
```



The probability mass function



The Poisson Distribution: what it is, and features

- $\sigma_Y^2 = \mu \rightarrow \sigma_Y = \sqrt{\mu}.$

The Poisson Distribution: what it is, and features

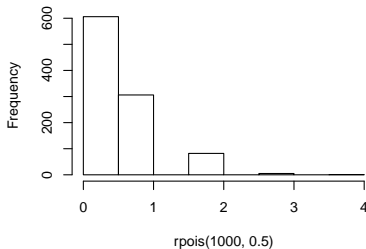
- $\sigma_Y^2 = \mu \rightarrow \sigma_Y = \sqrt{\mu}.$
- Approximated by $\mathcal{N}(\mu, \sqrt{\mu})$ when $\mu \gg 10$

The Poisson Distribution: what it is, and features

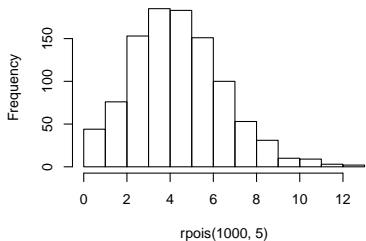
- $\sigma_Y^2 = \mu \rightarrow \sigma_Y = \sqrt{\mu}$.
- Approximated by $\mathcal{N}(\mu, \sqrt{\mu})$ when $\mu \gg 10$
- Open-ended (unlike Binomial), but in practice, has finite range.
- Poisson data sometimes called “numerator only”: (unlike Binomial) may not “see” or count “non-events”

Normal approximation to Poisson is the CLT in action

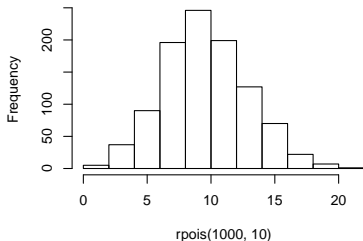
Histogram of rpois(1000, 0.5)



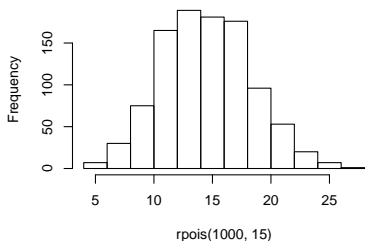
Histogram of rpois(1000, 5)



Histogram of rpois(1000, 10)



Histogram of rpois(1000, 15)



How it arises

- Count of events or items that occur randomly, with low homogeneous intensity, in time, space, or ‘item’-time (e.g. person-time).
- $\text{Binomial}(n, \pi)$ when $n \rightarrow \infty$ and $\pi \rightarrow 0$, but $n \times \pi = \mu$ is finite.
- $Y \sim \text{Poisson}(\mu_Y)$ if time (T) between events follows an $T \sim \text{Exponential}(\mu_T = 1/\mu_Y)$.

http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/Randomness_poisson.pdf

- As sum of ≥ 2 *independent* Poisson random variables, with same **or different** μ 's:
 $Y_1 \sim \text{Poisson}(\mu_1) \quad Y_2 \sim \text{Poisson}(\mu_2) \Rightarrow Y = Y_1 + Y_2 \sim \text{Poisson}(\mu_1 + \mu_2)$.

Poisson distribution as a limit

The rationale for using the Poisson distribution in many situations is provided by the following proposition.

Proposition (Limit of a binomial is Poisson)

Suppose that $Y \sim \text{Binomial}(n, \pi)$. If we let $\pi = \mu/n$, then as $n \rightarrow \infty$, $\text{Binomial}(n, \pi) \rightarrow \text{Poisson}(\mu)$. Another way of saying this: for large n and small π , we can approximate the $\text{Binomial}(n, \pi)$ probability by the $\text{Poisson}(\mu = n\pi)$.

Poisson approximation to the Binomial

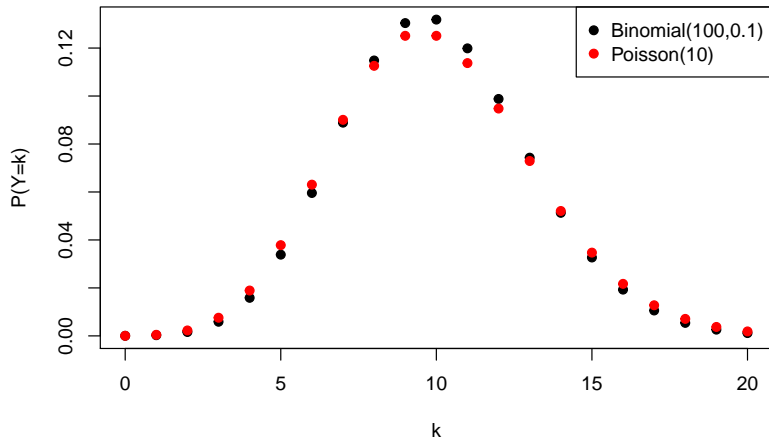


Figure: Probability mass function for $\text{Bin}(n=100, 0.1)$ and $\text{Poisson}(10)$

Examples

- numbers of asbestos fibres
- deaths from horse kicks*
- needle-stick or other percutaneous injuries
- bus-driver accidents*
- twin-pairs*
- radioactive disintegrations*
- flying-bomb hits*
- white blood cells
- typographical errors
- cell occupants – in a given volume, area, line-length, population-time, time, etc. ¹

¹* included in <http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/>

Confidence interval for μ

- If the CLT hasn't kicked in, then the usual CI might not be appropriate:

$$\text{point-estimate} \pm z^{\star} \times \text{standard error}$$

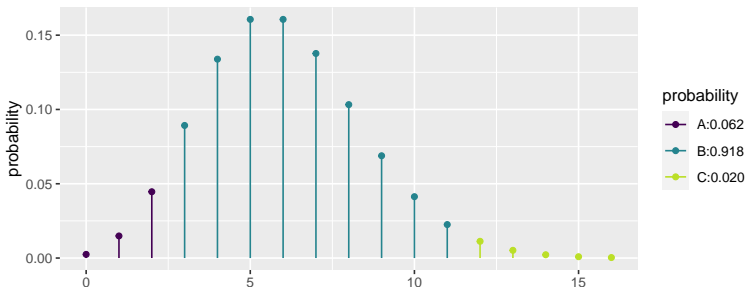
Confidence interval for μ

- If the CLT hasn't kicked in, then the usual CI might not be appropriate:

$$\text{point-estimate} \pm z^{\star} \times \text{standard error}$$

- `qpois` function doesn't work either:

```
# middle area is not 95%  
mosaic::xqpois(c(0.025, 0.975), lambda = 6)
```



```
## [1] 2 11
```

Confidence interval for μ

- Similar to the binomial (Clopper-Pearson CI), we consider a *first-principles* $100(1 - \alpha)\%$ CI $[\mu_{\text{LOWER}}, \mu_{\text{UPPER}}]$ such that

$$P(Y \geq y \mid \mu_{\text{LOWER}}) = \alpha/2 \quad \text{and} \quad P(Y \leq y \mid \mu_{\text{UPPER}}) = \alpha/2.$$

- For example, the 95% CI for μ , based on $y = 6$, is $[\underline{2.20}, \underline{13.06}]$.

LOWER
 $\mu = 2.2$

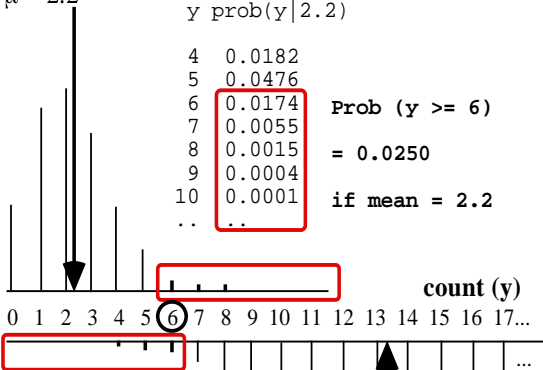
y prob(y|2.2)

4	0.0182
5	0.0476
6	0.0174
7	0.0055
8	0.0015
9	0.0004
10	0.0001
..	..

Prob (y >= 6)

= 0.0250

if mean = 2.2



y prob(y|13.06)

0	0.0000
1	0.0000
2	0.0002
3	0.0008
4	0.0026
5	0.0067
6	0.0147
7	0.0274

Prob (y <= 6)

= 0.0250

if mean = 13.06

UPPER
 $\mu = 13.06$

⑥ observed count

Poisson 95% CI for μ when $y = 6$

```
# upper limit --> lower tail needs 2.5%
manipulate::manipulate(
  mosaic::xppois(6, lambda = LAMBDA),
  LAMBDA = manipulate::slider(0.01, 20, step = 0.01))

# lower limit --> upper tail needs 2.5%
# when lower.tail=FALSE, ppois doesnt include k, i.e., P(Y > k)
manipulate::manipulate(
  mosaic::xppois(5, lambda = LAMBDA, lower.tail = FALSE),
  LAMBDA = manipulate::slider(0.01, 20, step = 0.01))
```

Confidence interval for μ

- For a given confidence level, there is one CI for each value of y .
- Each one can be worked out by trial and error, or – as has been done for the last 80 years – directly from the (exact) link between the tail areas of the Poisson and **Gamma** distributions.
- These CI's – for y up to at least 30 – were found in special books of statistical tables or in textbooks.
- As you can check, z-based intervals are more than adequate beyond this y . **Today**, if you have access to R (or Stata or SAS) you can obtain the first principles CIs directly **for any value of y** .

80%, 90% and 95% CI for mean count μ if we observe 0 to 30 events in a certain amount of experience

y	95%		90%		80%	
0	0.00	3.69	0.00	3.00	0.00	2.30
1	0.03	5.57	0.05	4.74	0.11	3.89
2	0.24	7.22	0.36	6.30	0.53	5.32
3	0.62	8.77	0.82	7.75	1.10	6.68
4	1.09	10.24	1.37	9.15	1.74	7.99
5	1.62	11.67	1.97	10.51	2.43	9.27
6	2.20	13.06	2.61	11.84	3.15	10.53
7	2.81	14.42	3.29	13.15	3.89	11.77
8	3.45	15.76	3.98	14.43	4.66	12.99
9	4.12	17.08	4.70	15.71	5.43	14.21
10	4.80	18.39	5.43	16.96	6.22	15.41
11	5.49	19.68	6.17	18.21	7.02	16.60
12	6.20	20.96	6.92	19.44	7.83	17.78
13	6.92	22.23	7.69	20.67	8.65	18.96
14	7.65	23.49	8.46	21.89	9.47	20.13
15	8.40	24.74	9.25	23.10	10.30	21.29
16	9.15	25.98	10.04	24.30	11.14	22.45
17	9.90	27.22	10.83	25.50	11.98	23.61
18	10.67	28.45	11.63	26.69	12.82	24.76
19	11.44	29.67	12.44	27.88	13.67	25.90
20	12.22	30.89	13.25	29.06	14.53	27.05
21	13.00	32.10	14.07	30.24	15.38	28.18
22	13.79	33.31	14.89	31.41	16.24	29.32
23	14.58	34.51	15.72	32.59	17.11	30.45
24	15.38	35.71	16.55	33.75	17.97	31.58

95% CI for mean count μ with q function

- To obtain these in R we use the natural link between the Poisson and the *gamma* distributions.²
- In R, e.g., the 95% limits for μ based on $y = 6$ are obtained as

```
qgamma(p = c(0.025,0.975), shape = c(6, 7))  
## [1] 2.2 13.1
```

- More generically, for *any* y , as

```
qgamma(p = c(0.025,0.975), shape = c(y, y+1))
```

² [details found here](#)

95% CI for mean count μ with canned function

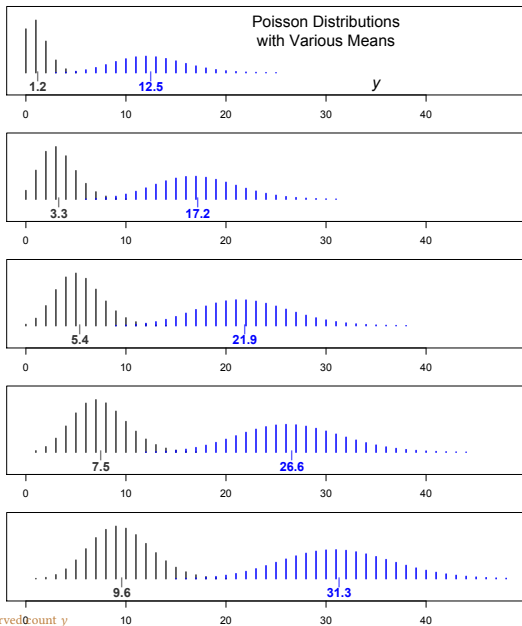
- These limits can also be found using the canned function in R

```
stats::poisson.test(6)

## Exact Poisson test with 6 time base: 1
## number of events = 6, time base = 1, p-value = 0.0005942
## alternative hypothesis: true event rate is not equal to 1
## 95 percent confidence interval:
##  2.2 13.1
## sample estimates:
## event rate
##      6
```

z-based confidence intervals

once μ is in the upper teens, the Poisson \rightarrow the Normal



z-based confidence intervals

- Thus, a plus/minus CI based on $SE = \hat{\sigma} = \sqrt{\hat{\mu}} = \sqrt{y}$, is simply

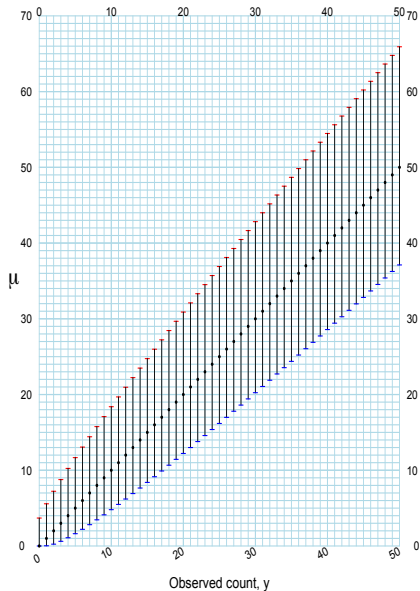
$$[\mu_L, \mu_U] = y \pm z^* \times \sqrt{y}.$$

- Equivalently we can use the q function:

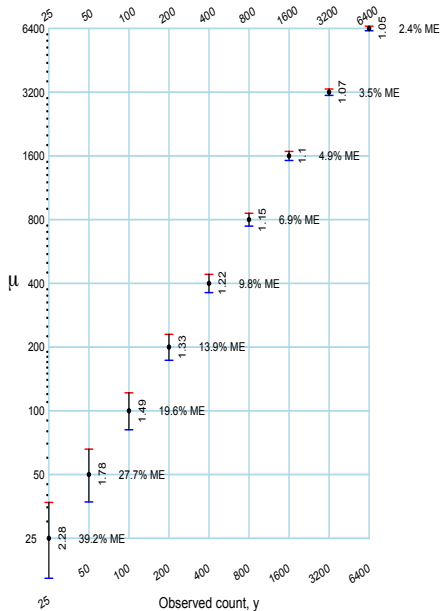
$$qnorm(p = c(0.025, 0.975), mean = y, sd = \sqrt{y})$$

- From a single realization y of a $N(\mu, \sigma_Y)$ random variable, we can't estimate **both** μ and σ_Y : for a SE, we would have to use *outside* information on σ_Y .
- In the Poisson(μ) distribution, $\sigma_Y = \sqrt{\mu}$, so we calculate a “model-based” SE.

95% CIs for μ



95% CIs for μ



Note

How is it that one can form a CI for μ from a single observation y ?

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How is it that one can form a CI for μ from a single observation y ?

- If we had a single realization y of a $\mathcal{N}(\mu, \sigma_Y)$ random variable, we could not, from this single y , estimate both μ and σ_Y
- However, the $Poisson(\mu)$ distribution is different in that $\sigma_Y = \sqrt{\mu}$ so we can calculate a **model-based** standard error from this relationship between the mean and the variance

Rates are better for comparisons

year	deaths (y)
1971	33
2002	211

Table: Deaths from lung cancer in the age-group 55-60 in Quebec in 1971 and 2002

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A researcher asks: Is the situation getting worse over time for lung cancer in this age group?

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Table: Deaths from lung cancer in the age-group 55-60 in Quebec in 1971 and 2002

A researcher asks: Is the situation getting worse over time for lung cancer in this age group?

Your reply: What's the denominator??

La Presse Sports

**Sutter a trop parlé;
personne ne va
toucher à Roy,
foi de Carbo**

Pages 2 à 5



Rates are better for comparisons

- So far, we have focused on inference regarding μ , the expected **number** of events in the amount of experience actually studied.
- However, for comparison purposes, the frequency is more often expressed as a **rate, intensity or incidence density (ID)**.

Rates are better for comparisons

- So far, we have focused on inference regarding μ , the expected **number** of events in the amount of experience actually studied.
- However, for comparison purposes, the frequency is more often expressed as a **rate, intensity or incidence density (ID)**.

year	deaths (y)	person-time (PT)	rate ($\hat{\lambda}$)
1971	33	131,200 years	25 per 100,000 women-years
2002	211	232,978 years	91 per 100,000 women-years

Table: Deaths from lung cancer in the age-group 55-60 in Quebec in 1971 and 2002

Rates are better for comparisons

- The *statistic*, the empirical rate or empirical incidence density, is

$$rate = \hat{ID} = \hat{\lambda} = y/PT.$$

- where y is the observed number of events and PT is the amount of Population-Time in which these events were observed.
- We think of \hat{ID} or $\hat{\lambda}$ as a point estimate of the (theoretical) Incidence Density *parameter*, ID or λ .

CI for the rate parameter λ

- To calculate a CI for the ID parameter, we **treat the PT denominator as a constant**, and the **numerator, y , as a Poisson random variable**, with expectation $E[y] = \mu = \lambda \times PT$, so that

$$\lambda = \mu \div PT$$

$$\hat{\lambda} = \hat{\mu} \div PT$$

$$= y \div PT$$

$$\boxed{\text{CI for } \lambda = \{\text{CI for } \mu\} \div PT.}$$

(1)

CI for the rate parameter λ

- $y = 211$ deaths from lung cancer in 2002 leads to a 95% CI for μ :

```
qgamma(p = c(0.025, 0.975), shape = c(211, 212))  
## [1] 183 241
```

CI for the rate parameter λ

- $y = 211$ deaths from lung cancer in 2002 leads to a 95% CI for μ :

```
qgamma(p = c(0.025, 0.975), shape = c(211, 212))  
## [1] 183 241
```

- From this we can calculate the 95% CI **per 100,000 WY** for λ using a PT=232978 years:

```
qgamma(p = c(0.025, 0.975), shape = c(211, 212)) / 232978 * 1e5  
## [1] 79 104
```

CI for the rate parameter λ

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qgamma(p = c(0.025, 0.975), shape = c(211, 212))  
## [1] 183 241
```

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```
qgamma(p = c(0.025, 0.975), shape = c(211, 212)) / 232978 * 1e5  
## [1] 79 104
```

- $y = 33$ deaths from lung cancer in 131200 women-years in 1971 leads to a 95% CI per 100,000 WY for λ of

```
qgamma(c(0.025,0.975), c(33,34)) / 131200 * 1e5  
## [1] 17 35
```

CI for the rate parameter λ using canned function

```
stats::poisson.test(x = 33, T = 131200)

## Exact Poisson test with 33 time base: 131200
## number of events = 33, time base = 131200, p-value < 2.2e-16
## alternative hypothesis: true event rate is not equal to 1
## 95 percent confidence interval:
##  0.00017 0.00035
## sample estimates:
## event rate
##    0.00025
```


Statistical evidence and the p -value

Recall:

- P-Value = $\text{Prob}[y \text{ or more extreme} \mid H_0]$
- With ‘more extreme’ determined by whether H_{alt} is 1-sided or 2-sided.
- For a **formal test**, at level α , compare this P-value with α .

Example: Cancers surrounding nuclear stations

- Cancers in area surrounding the Douglas Point nuclear station

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- Denote by $\{CY_1, CY_2, \dots\}$ the numbers of Douglas Point child-years of experience in the various age categories that were pooled over.
- Denote by $\{\lambda_1^{Ont}, \lambda_2^{Ont}, \dots\}$ the age-specific leukemia incidence rates during the period studied.

Example: Cancers surrounding nuclear stations

- Cancers in area surrounding the Douglas Point nuclear station
- Denote by $\{CY_1, CY_2, \dots\}$ the numbers of Douglas Point child-years of experience in the various age categories that were pooled over.
- Denote by $\{\lambda_1^{Ont}, \lambda_2^{Ont}, \dots\}$ the age-specific leukemia incidence rates during the period studied.
- If the underlying incidence rates in Douglas Point were the same as those in the rest of Ontario, the **E**xpected total number of cases of leukemia for Douglas Point would be

$$E = \mu_0 = \sum_{ages} CY_i \times \lambda_i^{Ont} = 0.57.$$

Example: Cancers surrounding nuclear stations

- Cancers in area surrounding the Douglas Point nuclear station
- Denote by $\{CY_1, CY_2, \dots\}$ the numbers of Douglas Point child-years of experience in the various age categories that were pooled over.
- Denote by $\{\lambda_1^{Ont}, \lambda_2^{Ont}, \dots\}$ the age-specific leukemia incidence rates during the period studied.
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Age Standardized Incidence Ratio (SIR) = $O/E = 2/0.57 = 3.5$.

Q: Is the $O = 2$ significantly higher than $E = 0.57$

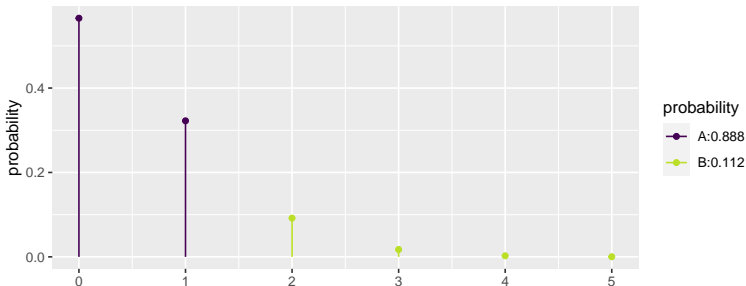
Question:

- Is the $y = 2$ cases of leukemia observed in the Douglas Point experience statistically significantly higher than the $E = 0.57$ cases “expected” for this many child-years of observation if in fact the rates in Douglas Point and the rest of Ontario were the same?
- Or, is the $y = 2$ observed in this community compatible with $H_0 : y \sim \text{Poisson}(\mu = 0.57)$?

A: Is the $O = 2$ significantly higher than $E = 0.57$

- Answer:** Under H_0 , the age-specific numbers of leukemias $\{y_1 = O_1, y_2 = O_2, \dots\}$ in Douglas Point can be regarded as independent Poisson random variables, so their sum y can be regarded as a single Poisson random variable with $\mu = 0.57$.

```
mosaic::xppois(1, lambda = 0.57, lower.tail = FALSE)
```



```
## [1] 0.11
```


95% CI for the SIR by hand

- To get the CI for the SIR, divide the CI for Douglas Point μ_{DP} by the null $\mu_0 = 0.57$ (Ontario scaled down to the same size and age structure as Douglas Point.) We treat it as a constant because the Ontario rates used in the scaling are measured with much less sampling variability than the Douglas Point ones.

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- The $y = 2$ cases translates to
 - ▶ 95% CI for $\mu_{DP} \rightarrow [0.24, 7.22]$
 - ▶ 95% CI for the SIR $\rightarrow [0.24/0.57, 7.22/0.57] = [0.4, 12.7]$.

95% CI for the SIR using canned function

- We can *trick* `stats::poisson.test` to get the same CI by putting time as 0.57:

```
stats::poisson.test(x=2,T=0.57)

## Exact Poisson test with 2 time base: 0.57
## number of events = 2, time base = 0.57, p-value = 0.1121
## alternative hypothesis: true event rate is not equal to 1
## 95 percent confidence interval:
##  0.42 12.67
## sample estimates:
## event rate
##      3.5
```

Session Info

```
R version 4.0.2 (2020-06-22)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Pop!_OS 20.04 LTS

Matrix products: default
BLAS:   /usr/lib/x86_64-linux-gnu/openblas-pthread/libblas.so.3
LAPACK: /usr/lib/x86_64-linux-gnu/openblas-pthread/liblapack.so.3

attached base packages:
[1] tools      stats      graphics  grDevices  utils      datasets  methods
[8] base

other attached packages:
[1] NCStats_0.4.7   FSA_0.8.30      forcats_0.5.0   stringr_1.4.0
[5] dplyr_1.0.2     purrr_0.3.4     readr_1.3.1     tidyr_1.1.2
[9] tibble_3.0.3    ggplot2_3.3.2   tidyverse_1.3.0 knitr_1.29

loaded via a namespace (and not attached):
[1] fs_1.5.0          lubridate_1.7.9   httr_1.4.2        latex2exp_0.4.0
[5] backports_1.1.9   R6_2.4.1          DBI_1.1.0          colorspace_1.4-1
[9] withr_2.2.0       tidyselect_1.1.0  gridExtra_2.3      leaflet_2.0.3
[13] curl_4.3          compiler_4.0.2    cli_2.0.2          rvest_0.3.6
[17] xml2_1.3.2        gg dendro_0.1.22  labeling_0.3       mosaicCore_0.8.0
[21] scales_1.1.1      digest_0.6.25     ggformula_0.9.4    foreign_0.8-79
[25] rio_0.5.16        pkgconfig_2.0.3   htmltools_0.5.0    dbplyr_1.4.4
[29] highr_0.8         htmlwidgets_1.5.1 rlang_0.4.7        readxl_1.3.1
[33] rstudioapi_0.11   farver_2.0.3      generics_0.0.2     jsonlite_1.7.1
[37] crosstalk_1.1.0.1 zip_2.1.1         car_3.0-9          magrittr_1.5
[41] mosaicData_0.20.1 Matrix_1.2-18     Rcpp_1.0.5         munsell_0.5.0
[45] fansi_0.4.1       abind_1.4-5       lifecycle_0.2.0    stringi_1.5.3
[49] carData_3.0-4     MASS_7.3-53       plyr_1.8.6         ggstance_0.3.4
[53] grid_4.0.2        blob_1.2.1        ggrepel_0.8.2      crayon_1.3.4
[57] lattice_0.20-41   haven_2.3.1       splines_4.0.2      hms_0.5.3
[61] pillar_1.4.6      reprex_0.3.0      glue_1.4.2         evaluate_0.14
[65] data.table_1.13.0 modelr_0.1.8       vctrs_0.3.4        tweenr_1.0.1
[69] cellranger_1.1.0  gtable_0.3.0      polyclip_1.10-0    assertthat_0.2.1
[73] TeachingDemos_2.12 xfun_0.17         ggforce_0.3.2      openxlsx_4.1.5
[77] broom_0.7.0       viridisLite_0.3.0 mosaic_1.7.0        ellipsis_0.3.1
```