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

Contents...

[1] See also: derivation & applications (counting yeast cells in beer) in Student's 1907 paper http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/Student_counting.pdf "On the Error of Counting with a Haemacytometer"; and Ch. from Armitage et al.

[2] cf. http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/Randomness_poisson.pdf "Randomness at the root of things: Poisson sequences".

1 (Poisson) Model for (Sampling)Variability of a Count in a given amount of "experience"

The Poisson Distribution: what it is, and some of its features

- The (infinite number of) probabilities $P_0, P_1, ..., P_y, ...$, of observing $Y = 0, 1, 2, \ldots, y, \ldots$ "events"/"instances" in a given amount of "experience."
- These probabilities, $Prob[Y = y]$, or $P_Y[y]$'s, or P_y's for short, are governed by a single parameter, the mean $E[Y] = \mu$.
- $P[y] = \exp[-\mu]\, \mu^y / y!$ {note recurrence relation: $P_y = P_{y-1} \times (\mu/y)$.}
- Shorthand: $Y \sim$ Poisson(μ).
- $Var[Y] = \mu$; i.e., $\sigma_Y^2 = \mu_Y$.
- Approximated by $N(\mu,\, \sigma_Y = \mu^{1/2})$ when $\mu >> 10$.
- 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": but there is (an invisible) denominator "behind' the no. of "wrong number" phone calls you receive.

How it arises / derivations

- Count of events (items) that occur randomly, with low homogeneous intensity, in time, space, or 'item'-time (e.g. person–time).
- Binomial(n, π) when $n \to \infty$ and $\pi \to 0$, but $n \times \pi = \mu$ is finite.
- $Y \sim Poisson(\mu_Y) \Leftrightarrow T$ time b/w events $\sim$ Exponential($\mu_T = 1/\mu_Y$). http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/Randomness_poisson.pdf
- As sum of ≥ 2 *independent* Poisson rv's, with same **or different** μ's: $Y_1 \sim$ Poisson(μ_1) $Y_2 \sim$ Poisson(μ_2) $\Rightarrow Y = Y_1 + Y_2 \sim$ Poisson($\mu_1 + \mu_2$).
- **Examples**: numbers of asbestos fibres, deaths from horse kicks*, needlestick or other percutaneous injuries, bus-driver accidents*, twin-pairs*, radioactive disintegrations*, flying-bomb hits*, white blood cells, typographical errors, "wrong numbers", cancers; chocolate chips, radioactive emissions in nuclear medicine, cell occupants – in a given volume, area, line-length, population-time, time, etc. [* included in http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/]

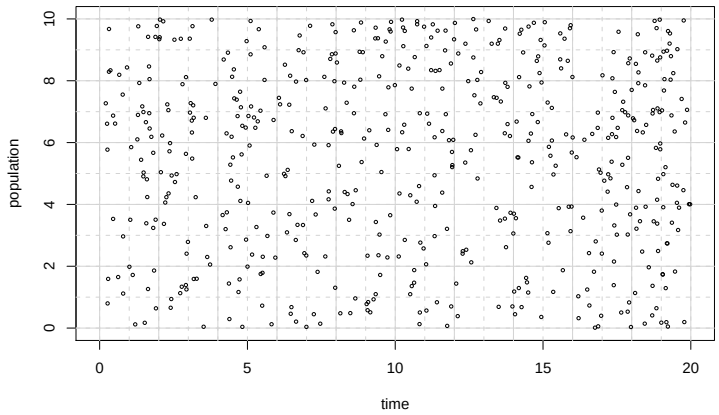

Figure 1: Events in Population-Time.. randomly generated from intensities that are constant within (2 squares high by 2 squares wide) 'panels', but vary between such panels. In Epidemiology, each square might represent a number of units of population-time, and each dot an event.

1.1 Does the Poisson Distribution apply to.. ?

- Yearly variations in numbers of persons killed in plane crashes? [3]
- Daily variations in numbers of births?[4]
- Daily variations in no.s of deaths [variation over the seasons]
- Daily variations in numbers of traffic accidents [variation over the seasons, and days of week, and with weather etc.]
- Daily variations in numbers of deaths in France in summer 2002 & 2003[5]

[3] Yearly variations in no.s of plane *crashes* may be closer to Poisson [apart from variation due to improvements in safety, fluctuations in numbers of flights etc].

[4] See e.g. Number of weekday and weekend births in New York in August 1966 on web page: the variations are closer to Poisson if use *weekly* count.

[5] c.f. Impact sanitaire de la vague de chaleur en France survenue en août 2003. Rapport d'étape 29 aot 2003 [on course webpage] and Vanhems P et al. Number of in-hospital deaths at Edouard Herriot Hospital ,and Daily Maximal Temperatures during summers of 2002 and 2003, Lyon, France. New Eng J Med Nov 20, 2003, pp2077-2078. ibid. see Resources.

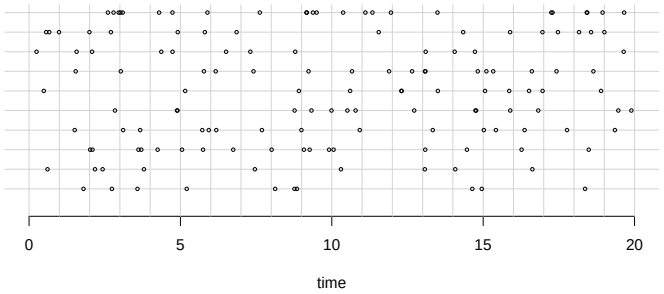

Figure 2: Events in Time: 10 examples, randomly generated from constant over time intensities. Simulated with 1000 Bernoulli($_{\text{small}}\,\pi$)'s per time unit.

- Variations across cookies/pizzas in numbers of chocolate chips/olives.
- Variations across days of year in numbers of deaths from sudden infant death syndrome.

1.2 Calculating Poisson probabilities:

1.2.1 Exactly

- pdf: formula for P_y (or recursion $P[y] = \frac{\mu}{y} \times P[y-1];\ P[0] = \exp[-\mu]$).
- cdf:
  - Summation of terms in pdf
  - Using link between this sum and the cdf of χ^2 Distribution[6].
- Spreadsheet — Excel function `POISSON`(y, μ, cumulative)
- `R`: `dpois(), ppois(), qpois()` mass/distribution/quantile
  `SAS`: `POISSON`;
  `Stata`: cf. `www.ats.ucla.edu/ stat/stata/faq/pprob.htm` 'how to'. ;

[6] Fisher 1935: see Resources

1.2.2 Using Gaussian Approximations to distribution of y or transforms of it

Described below, under Inference.

2 Inference re μ, based on observed count y

2.1 "First Principles" Confidence Interval

By first-principles $100(1-\alpha)\%$ CI, we mean "not usual point-estimate $\pm$ some multiple of standard error," but rather the pair $(\mu_{LOWER}, \mu_{UPPER})$ such that

$$P(Y \geq y \,|\, \mu_{LOWER}) = \alpha/2 \;\; \& \;\; P(Y \leq y \,|\, \mu_{UPPER}) = \alpha/2.$$

2.1.1 Exact – see Figure 3 for example, based on $y = 6$

Tables: For a given α, there is just one CI for each value of y; these exact CI's have been extensively tabulated and made available in several texts and Tables, e.g., the Documenta Geigy, and Biometrika Tables for Statisticians.[7]

If don't have tables... Can find exact lower and upper limits $\mu_{LOWER/UPPER}$ that yield the target $\alpha/2$'s either by **trial & error** (rapidly with software that evaluates Poisson tail areas) or **directly** using the Link between the tail areas of the Poisson and tail areas of Chi- Square distributions (full details in article by Fisher, 1935, under Resources on webpage), $\mu_{LOWER} = \frac{1}{2}\chi^2_{2y,\alpha/2}$, $\mu_{UPPER} = \frac{1}{2}\chi^2_{2y+2,1-\alpha/2}$. Some specialized software packages (eg in `R`) also have functions that provide them directly.[8]

2.1.2 Quite accurate approximation to exact tail area

Using Wilson-Hilferty approximation to Chi-square quantiles[9] This has high accuracy for $y > 10$; it uses z, the normal standardized variate

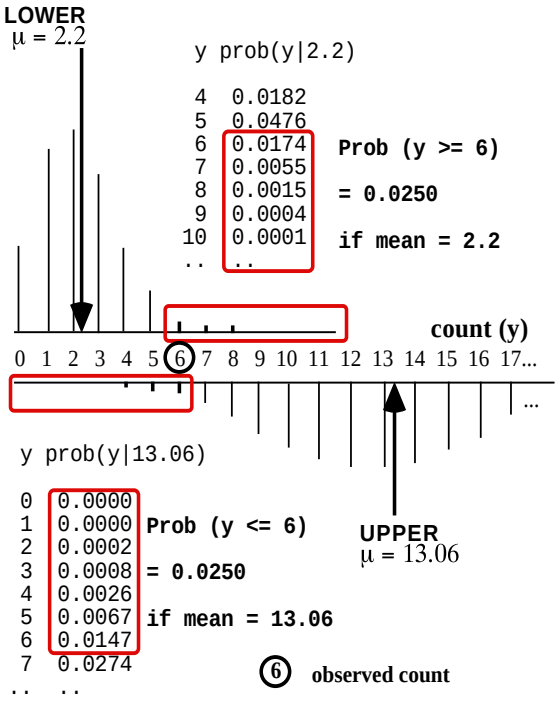

Figure 3: Example of Exact 95% CI of $\{2.2, 13.06\}$ for μ, based on $y = 6$.

corresponding to $\alpha/2$, e.g., $\alpha = 0.10 \rightarrow z = 1.645; \alpha = 0.05 \rightarrow z = 1.96,$ etc.

$$\mu_{LOWER} = y \times \{1 - [9y]^{-1} - z \times [9y]^{-1/2}\}^3$$

$$\mu_{UPPER} = (y+1) \times \{1 - [9(y+1)]^{-1} + z \times [9(y+1)]^{-1/2}\}^3$$

2.1.3 Not quite as accurate an approximation, but 1st principles

Using $Y \simeq N(\mu,\, \sigma = \mu^{1/2})$:

[7] (See (homemade) "Confidence limits for the expectation [i.e. the 'mean' parameter] of a Poisson random variable" on last page and (more fully) under Resources.

[8] Note that the above "First Principle" is a *general* and important one; it "just so happens" that in this particular discrete distribution, if one has access to the percentiles of the Chi-Square distribution, the link helps avoid the trial and error process involved.

[9] Rothman[2002], page 134, provides an adaptation from "D. Byar, unpublished" in which he makes a further approximation, using the average $(y + 0.5)$ for both the lower an upper limits, rather than the more accurate y for the lower and $y + 1$ for the upper limit. JH is surprised at Rothman's eagerness to save a few keystrokes on his calculator, and at his reference to an unpublished source, rather than the 1931 publication of Wilson and Hilferty. The Full Wilson and Hilferty citation, and evaluation of the above equation, can be found in Liddell's article "Simple exact analysis of the standardized mortality ratio" in J Epi and Comm. Health 37 85-88, 1984, available on website.

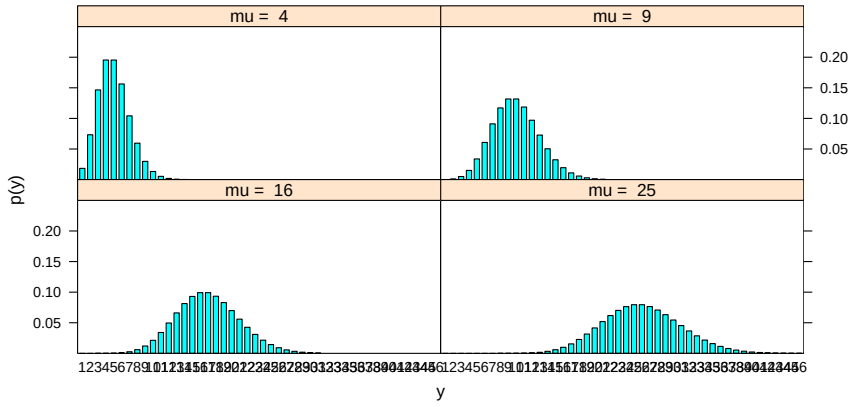

Figure 4: Poisson Distributions, over range $y = 0$ to 40, corresponding to $\mu = 4,\ 9,\ 16,$ and 25.

Obtained by solving the two equations:

$$y = \mu_{LOWER} + z \times \{\mu_{LOWER}\}^{1/2} \ ; \ y = \mu_{UPPER} - z \times \{\mu_{UPPER}\}^{1/2}$$

to give

$$\mu_{LOWER,UPPER} = ([y + z^2/4]^{1/2} \mp z/2)^2.$$

2.1.4 Variance-stabilizing transformation, so first principles

With μ large enough, $Y^{1/2} \sim (approx) N(\mu^{1/2},\ \sigma = 1/2)$, i.e., the SD is independent of $\mu^{1/2}$, thus providing for a first-principles interval:

$$\mu_{LOWER,UPPER} = y \mp z \times c^{1/2} + (z/2)^2.$$

2.2 "Not First Principles" Confidence Intervals, based on SE calculated at point estimate

2.2.1 Based on $Y \simeq N(\mu,\ \hat{\sigma} = y^{1/2})$.

If lazy, or don't care about principles /accuracy, or if y is large, can solve

$$y = \mu_{LOWER} + z \times y^{1/2} \ ; \ y = \mu_{UPPER} - z \times y^{1/2}$$

to give

$$\mu_{LOWER,UPPER} = y \mp z \times y^{1/2}.$$

"Large-n": How Large is large?: The same rule of thumb: when expected no. of events, $\mu = E[Y] > 5$. or the same JH rule: when the tables don't go as high as your value of y. It works well if the distribution is not 'crowded' into the left corner (cf. Figure 3), i.e., if, with the symmetric Gaussian approximation, the lower tail of the distribution does not spill over the 0 boundary.

The above model is used if one fits a **generalized linear model**, with Poisson error but **IDENTITY link**. Example with $y = 4$:

e.g. In SAS:

```
PROC GENMOD; model y = /  dist = POISSON link = IDENTITY WALFCI;
```

e.g. In Stata

```
input y
1 * glm doesn't like file with 1 'observation'
3 *so ..... split across 2 'observations'
end
glm y , family (poisson) link (identity)
```

e.g. In R: `y=4; summary(glm(y ~ 1,family=poisson (link=identity) ))`

2.2.2 Based on $\log Y \simeq N(\log[\mu],\ \hat{\sigma} = \{1/\hat{\mu}\}^{1/2})$

- **Derivation:**

  Use the "Delta Method" to derive the approximate variance for the random variable $\log Y$, assuming that Prob$[Y = 0]$ is negligible.

  $\text{Var}[\log Y] \approx \text{Var}[Y] \times \{(d \log Y/dY)|_{Y=\mu_Y}\}^2 = \mu \times (1/\mu_Y)^2 = 1/\mu_Y.$

  We will make a lot of use of this result, especially for the variance of the log of a rate, and for the variance of the **log of a rate ratio** (i.e., the variance of the difference of two log rates).

  (Empirical) *rate ratio(rr)* or *id*[10] *ratio (idr)*: $\hat{\lambda}_2 \div \hat{\lambda}_2 = \frac{y_2}{PT_2} \div \frac{y_1}{PT_1}$

$$\begin{aligned} Var[\log(rr)] &= Var[\log y_2 - \log y_1] \\ &= Var[\log y_2] + Var[\log y_1] \\ &= 1/\mu_2 + 1/\mu_1. \\ &= 2 \div \{ \text{ Harmonic Mean of } \mu_2 \text{ and } \mu_1\} \end{aligned}$$

[10] incidence density

- **CI:** $\exp[\log(y) \mp z \times (1/y)^{1/2}]$. **e.g., ...**

  In R: `summary(glm(y ~ 1,family=poisson(link=log) ))`

  In SAS: `MODEL y = / dist = POISSON link = LOG WALFCI;`

  In Stata: `glm y , family (poisson) link (log)`

3 Applications, and Notes

3.1 How large a count so that margin of error $< 15\%$?

An estimate of WBC concentration can be made by manually counting enough fields (n) until say a total of $y = 200$ cells have been observed. This is not quite a Poisson distribution since $y = 200$ is fixed ahead of time and n is the random variable – but the variability in the estimate $200/n$ is close to Poisson-based, so as a first approximation we will treat the y as the variable and the denominator n as fixed. The estimate has margins of error (ME) of 13% and 15% – since [as one can derive from trial and error] a total count of 200 (marked by ↑ below) could be a *high* reading from a concentration which produces a μ of 173 (for the same n), or a *low* reading from a concentration which produces an average of $\mu = 230$, i.e.

y `per` n: `160..170..180..190..`***200***`..210..220..230..240...`

$\ldots\ldots\ldots\ldots\ldots\mu_L\ldots\ldots\ldots\ldots\uparrow\ldots\ldots\ldots\ldots\mu_U\ldots\ldots$

$\ldots\ldots\ldots\ldots\ldots\ldots$***200*** $= 173 + 1.96 \times \{173\}^{1/2}\ldots\ldots\ldots\ldots$

$\ldots\ldots\ldots\ldots\ldots\ldots$***200*** $= 230 - 1.96 \times \{230\}^{1/2}\ldots\ldots\ldots\ldots$

3.2 Leukemia Rate Triples near Nuke Plant: Study

OTTAWA (CP)[11] - Children born near a nuclear power station on Lake Huron have 3.5 times the normal rate of leukemia, according to figures made public yesterday. The study conducted for the Atomic Energy Control Board, found the higher rate among children born near the Bruce generating station at Douglas Point. But the scientist who headed the research team cautioned that the sample size was so small that that actual result could be much lower - or nearly four times higher.

Dr. Aileen Clarke said that while the Douglas Point results showed 3.5 cases of leukemia where one would have been normal[12], a larger sample size could place the true figure somewhere in the range from 0.4 cases to 12.6 cases.[13]

Clarke will do a second study to look at leukemia rates among children aged five to 14. The first study was on children under age 5. Clarke was asked whether parents should worry about the possibility that childhood leukemia rates could be over 12 times higher than normal around Douglas point. "My personal opinion is, not at this time," she said. She suggested that parents worried by the results should put them in context with other causes of death in children.

"Accidents are by far and away the chief cause of death in children, and what we're talking about is a very much smaller risk than that of death due to accidents," she said.

The results were detailed in a report on a year-long study into leukemia rates among children born within a 25-kilometre radius of five Ontario nuclear facilities. The study was ordered after British scientists reported leukemia rates among children born near nuclear processing plants were nine times higher than was normal. The Ontario study was based on 795 children who died of leukemia between 1950 and 1986 and 951 children who were diagnosed with cancer between 1964 and 1985.

It showed a lower-than-normal rate among children born near the Chalk River research station and only slightly higher than expected rates at Elliot Lake and Port Hope, uranium mining and conversion facilities.

At the Pickering generating station, the ratio was slightly higher still, at 1.4 - meaning there were 1.4 cases for every expected case. But the confidence interval - the range of reliability - for that figure set the possible range between 0.8 cases and 2.2 cases.[14]

Comment: It is interesting that it is the more extreme, but much less precise, SIR of 3.5, based on $O = 2, E = 0.57$ that made the headline, while the less extreme, but much more precise, SIR of 1.4, based on $O = 18, E = 12.8$, was relegated to the last paragraph.

[11] Montreal Gazette, Friday May 12, 1989.

[12] $SIR = 3.5 = No.Observed/No.Expected$. It is not $O = 3.5, E = 1$, since one cannot observe a fractional number of cases): SIR = 3.5; she simply scaled the O and the E so that E (reference "rate") is 1

[13] CI = (CI derived from O)/Expected = 0.4 to 12.6 (a 31-fold range). O is an integer. By trial and error, starting with O=1, and "trying all the CI's on for size" until one gets a 31-fold range, one comes to $O = 2$. (CI 0.242 to 7.22, range 31 fold). Dividing 2 by 3.5 gives an E of 0.57. Check: 95% CI for SIR (0.242 to 7.22) / 0.57 = 0.4 to 12.6.

[14] $SIR = 1.4 = O/E; CI = (CI$ derived from $O)/E$ has 0.8 to 2.2. This 2./0.8= 2.75-fold uncertainty comes from uncertainty generated by O. Examine range of 95% CI associated with each possible value of O, until come to 10.67 to 28.45 when $O = 18$. Divide 18 by 1.4 to get $E = 12.8$. Check 95% CI 10.67 to 28.45)/12.8 = 0.8 to 2.2.

3.3 Self-reported Percutaneous Injuries in Interns

Table 1. Rates of Percutaneous Injuries by Residency Program.[15]

Type of Residency	No. of Intern-Months	No. of Percutaneous Injuries	Rate (95% CI*) per Intern-Month
All	17003	498	0.0293 (0.0268-0.0318)
Internal medicine	3995	57	0.0143 (0.0106-0.0179)
Surgery	1730	124	0.0717 (0.0595-0.0838)
Family medicine	2008	51	0.0254 (0.0185-0.0323)
Emergency medicine	1007	40	0.0397 (0.0277-0.0518)
Pediatrics	2159	24	0.0111 (0.0067-0.0155)
Psychiatry	658	1	0.0015 (0.0000-0.0045)
Pathology	283	15	0.0530 (0.0269-0.0791)
Obstetrics/gynecology	964	94	0.0975 (0.0788-0.1160)
Other specialties	4199	92	0.0219 (0.0175-0.0263)

*Method not specified, but $\{498 \mp 498^{1/2}\} \div 17003 = \{0.0267, 0.0318\}$.

3.4 Cell Occupancy, Lotto 6/49, the Extremal Quotient, and Geographical Variation in Surgery Rates

What do these have in common? The answer may be easier to understand after seeing a few runs of the Excel Macro for visits to cells (in Resources).

3.5 Note: How is it that one can form a CI for μ from a *single* observation y? [Model-based CIs]

If we had a single realization y of a $N(\mu, \sigma_Y)$ random variable, we could not, from this single y, estimate **both** μ and σ_Y: one would have to rely on *outside* information concerning σ_Y. However, the Poisson(μ) distribution is different in that $\sigma_Y = \mu^{1/2}$, so we can calculate a "model-based" SE (or SE's if use a first principles CI) from this relationship between the mean and the variance.

Another way to understand why a SE is possible without going "outside" is to take advantage of the "divisibility" of a Poisson denominator, and its corresponding numerator.

We can split up the overall sample or slice of experience into (n) small enough sub samples so that the subcount y_i in each sub sample will be either a 0 or a 1 The (unit) variance of the observed sub counts should be $p(1-p)$ where p is the proportion of sub counts that are 1. Thus the estimated variance of the total count $y = \sum_i y_i$ should be n times the unit variance, or $n \times p(1-p)$. But if p is small, so that $1-p$ is near unity, then the variance of the sub count is approximately $n \times p$, which is simply the observed overall count y. i.e. the variance of a Poisson variable is equal to its mean. see more under Resources.

The sum of independent Poisson r.v.'s with different expectations is still a random variable with a Poisson distribution. The same is not true of a sum of independent Bernoulli (or Binomial) r.v.'s with different expectations.

If you were told that $Y_1 \sim$ Bernoulli($\pi_1 = 0.1$) and $Y_2 \sim$ Bernoulli($\pi_2 = 0.7$), you would not argue that the distribution of $Y = Y_1 + Y_2$ is Binomial($n = 2, \pi = 0.4$). You can check that yes, E(Y) = 0.8, but that $P_0 = 0.27$, $P_1 = 0.66$, $P_2 = 0.07$, much more concentrated than the Binomial(2,0.4) probabilities $P_0 = 0.36$, $P_1 = 0.48$, $P_2 = 0.16$.

BUT, what if you were told that $Y_1 \sim$ Poisson($\mu_1 = 0.1$) and $Y_2 \sim$ Poisson($\mu_2 = 0.7$). Would you argue that the distribution of $Y = Y_1 + Y_2$ is Poisson($\mu = 0.8$)? You can check that in fact it is.

In epidemiology, prevalence and other proportion-type statistics have denominators made up of (indivisible) individuals; the *person* is the statistical atom. However, when dealing with incidence density statistics, the denominators are made up of an infinite number of *person-moments.*

3.6 CI for Rate or Incidence Density parameter, ID (λ)

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**, or **intensity**. e.g., we convert $y = 211$ deaths from lung cancer in 232978 women-years (WY) in the age-group 55-60 in Quebec in 2002 into a rate or incidence density of 211/(232,978WY) = 0.00091/WY or **91** per 100,000WY. This makes it easier to compare the rate with the rate in the same age group in 1971, namely 33 lung cancer deaths in 131200WY, or 0.00025/WY = **25** per 100,000WY.

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

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

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 id or $\hat{ID}$ or $\hat{\lambda}$ as a point estimate of the (theoretical) Incidence Density *parameter*, ID or λ.

[15] Ayas NT, et al. JAMA. 2006;296:1055-1062 `http://www.epi.mcgill.ca/hanley/bios601/Intensity-Rate/NeedleStickSleep.pdf`

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

$$\lambda = \mu \div \text{PT},$$

$$\hat{\lambda} = \hat{\mu} \div \text{PT} = y \div \text{ PT},$$

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

The $y = 211$ leads to a (large-sample, SE-based)

$$95\% \text{ CI for } \mu: \ 211 \mp 1.96 \times 211^{1/2} \Rightarrow 211 \mp 28.5 \Rightarrow \{182.5, 239.5\}$$

$$95\% \text{ CI for } \lambda: \ \{182.5, 239.5\} \div 232,978\text{WY} \Rightarrow \{\mathbf{78.3}, \mathbf{102}\} \text{ per } 100,000\text{WY}$$

Whereas it matters little which method – exact or approximate – to use for the 95% CI from the 2002 data, the number of deaths in 1971 is a much smaller $y = 33$. Thus we will use the exact first principles CI for μ. The available tables stop at $y = 30$, so we will use the Excel spreadsheet, in the Resources, with a count of 33. It yields lower and upper limits of 22.7 and 46.3. Thus, to accompany the point estimate of 25 per 100,000WY, we have

$$95\% \text{ CI for } \lambda: \ \{22.7, 46.3\} \div 131,200\text{WY} \Rightarrow \{\mathbf{17.3}, \mathbf{35.3}\} \text{ per } 100,000\text{WY}$$

4 Test of $H_0 : \mu = \mu_0$, i.e. $\lambda = \lambda_0$.

Evidence: P-Value = Prob[y or more extreme | H_0], with 'more extreme' determined by whether H_{alt} is 1-sided or 2-sided.

For **formal test**, at level α, compare this P-value with α.

Examples:

1. **Cancers at Douglas Point**:

   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

   $$E = \mu_0 = \sum_{ages} CY_1 \times \lambda_i^{Ont} = 0.57.$$

   The actual total number of cases of leukemia ***O***bserved in Douglas Point was

   $$O = y = \sum_{ages} O_i = 2.$$

   So, (age-) *Standardized Incidence Ratio (SIR)* $= O/E = 2/0.57 = 3.5$.

   Q: 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: Since, under H_0, the age-specific numbers of leukemias $\{y_1 = O_1, y_2 = O_2, \dots\}$ in Douglas Point can be regared as independent Poisson random variables, their sum y can be regarded as a single Poisson random variable with $\mu = 0.57$. Thus we can calculate $P = Prob[Y \geq y \mid \mu = 0.57] = P[2] + P[3] + \dots$, i.e.

   $$P_{uppertail} = 1 - \{P[0] + P[1]\} = 1 - \{\ exp[-0.57] \times (1 + 0.57/1!)\} = 0.11.$$

   At the **Pickering** generating station, the **O**bserved number was **18**, versus an **E**xpected of **12.8**, for an *SIR* of 1.4. These larger numbers give us a chance to compare the *uppertail* P-values obtained by the exact method, i..e. $P = \sum_{y \geq 18} \text{PoissonProb}[y \mid \mu_0 = 12.8]$ with those obtained from various **approximations** to the Poisson($\mu_0 = 12.8$) distribution:-

   - Exactly $P = \text{Poisson Prob}[18|12.8] + P[19|12.8] + \dots = 0.099$
   - No (dis)-continuity correction: $P = \text{Prob}[Z \geq \frac{18-12.8}{12.8^{1/2}}] = 0.073$
   - No (dis)-continuity correction: $P = \frac{1}{2}\text{Prob}[\chi^2 \geq \frac{(18-12.8)^2}{12.8}] = 0.073$
   - No correction: [16] $P = \text{Prob}[Z \geq \log(18/12.8)/\{1/12.8\}^{1/2}] = 0.111$
   - No correction: [17] $P = \text{Prob}[Z \geq (18^{1/2} - 12.8^{1/2})/0.5] = 0.092$
   - With the correction: $P = \text{Prob}[Z \geq \frac{|18-12.8|-0.5}{12.8^{1/2}}] = 0.094$
   - With the correction: $P = \frac{1}{2}\text{Prob}[Z \geq \frac{(|18-12.8|-0.5)^2}{12.8}] = 0.094$

[16] Using $\log y \simeq N(\log \mu,\ \sigma = (1/\mu)^{1/2})$.
[17] Using $y^{1/2} \simeq N(\mu^{1/2},\ \sigma = 1/2)$.

2. "**Cluster of Events**" Story in *Montreal Gazette* in May 1989[18]

> Double Trouble in Moose Jaw School
> *(caption to a photograph showing 6 sets of twins)*
> Every morning, teachers at Prince Arthur school in Moose Jaw, Saskatchewan see double – and its not because of what they were up to the night before. Six pairs of identical twins attend the school, which has an enrollment of 375. Identical births occur once in 270 births.

What is the probability P of having 6 or more sets of twins in a school of size $n = 375$, when the twinning probability is $\pi = 1/270$?

This can be obtained with the Binomial(n, π) distribution; because n is large and π is small, the distribution can be approximated by the Poisson(μ) distribution, where $\mu = n \times \pi = 1.3$.

$$P = P[Y \geq 6] = 1 - P[Y \leq 5],$$

i.e., as

$$1 - \exp[-1.3] \times \{1 + 1.3/1! + 1.3^2/2! + 1.3^3/3! + 1.3^4/4! + 1.3^5/5!\} = 0.0022.$$

Thus, the probability is low that **this particular school** would have six or more sets. BUT, on average, in 1000 schools of this size, there will be 2.2 with this many or more. Thus, if we scan over a large number of such schools, finding **some school somewhere** with this extreme a number is not difficult. If the newswires scanned a large number of schools in 2007, there is a good chance the Montreal Gazette could re-use the headline – but they would have to change "Moose Jaw" to "Town X", with "X" to be filled in.

Moral: The Law of Large Numbers at play here is the same as the one in the video display terminals and miscarriages" story. *Natural "clusters" do occur by chance alone*, and distinguishing ones caused simply by chance from ones caused by some environmental or other such factor is not an easy task.

3. (Large-sample) Example: Where does the $O = 78$ cases of cancer in the "Sour Gas" community of Alberta fall relative to $E = 85.9$ "expected" for "non-sour-gas" communities with the same person years of experience and at Alberta cancer rates?

[18] See Hanley JA "Jumping to coincidences: defying odds in the realm of the preposterous". the American Statistician, 1992, 46(3) 197-202. – here `http://www.epi.mcgill.ca/hanley/Reprints/jumping_to_coincidences.pdf`

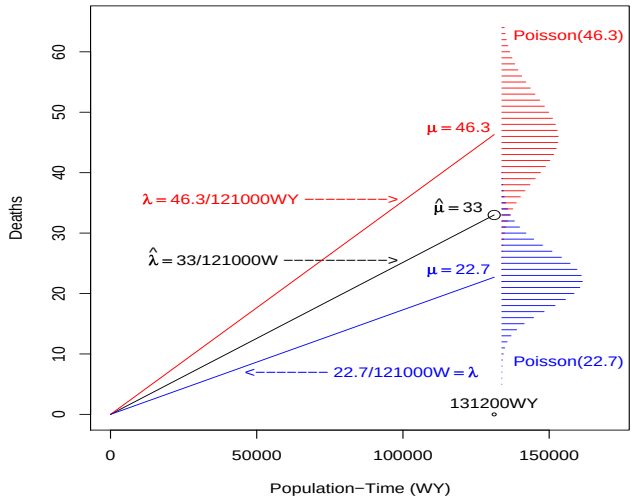

Figure 5: Depiction of empirical lung cancer mortality rate in age-group 55-60 in Quebec in 2002 as the slope of the line joining the point ($Y = 0$ cases, $PT = 0WY$) and the point ($Y = 33, PT = 121300WY$). Also shown are the Poisson Distributions, with $\mu_{UPPER} = 46.3$ and $\mu_{LOWER} = 22.7$ respectively, such that Prob$[Y \geq 33 \mid \mu = 22.7 =$ Prob$[Y \leq 33 \mid \mu = 46.3 = 0.025$.

5 Modelling Incidence Densities, or Rates, (λ's) via regression

Figure 5 (above) is a simple mathematical reversal of the fundamental epidemiologic definition of an empirical rate or incidence density (id)

$rate = id = \frac{\text{number of cases}}{\text{amount of population-time that generated these cases}}$, i.e., number of cases $= rate \times$ amount of population-time. There is a corresponding equation for the **expected** number of cases, in terms of the **theoretical rate,** λ: **E**[number of cases] = ***theoretical rate*** $\times$ amount of population-time.

This re-statement has 2 important implications (i) ***in epidemiology, we are students of rates*** and (ii) Generalized ***Linear Models (GLMs) allow us to fit equations of this very type***. Even though we put the numbers of cases on the left hand side of the regression equation, these GLMs allow us to express the theoretical rates (the focus of our investigations) as functions of the determinants of interest (e.g. age, smoking, diet, calendar time, treatment, ... etc) while treating the amounts of population time as constants that are of no intrinsic interest. In the lung cancer mortality dataset, we could have a (no. deaths, PT) 'data point' for every 'covariate pattern' or x-vector.

The two most common theoretical rate models are the additive and multiplicative forms:- ***rate***$[x] = \beta_0 + \beta_1 x$ & ***rate***$[x] = \exp(\beta_0 + \beta_1 x)$.

6 Planning: Sample Size for CIs and Tests

6.1 Precision

Even though it is tempting to specify the 'sample size' in terms of the Amount of Experience that needs to be studied to achieve this precision, ultimately the precision is governed by **the number of events**. So it is safer to specify sample size in these terms.

6.2 Amount of experience required to achieve a specified Coefficient of Variation (CV) for an estimated rate

See the example of the number of cells needed to count: approx. 200 so that have a margin or error of 15%.

6.3 Power – to detect Rate Ratio $RR = E_{alt}/E_0$

Exactly, using a spreadsheet or `R`:

Approximately, using a Gaussian approximations to $Poisson(\mu = E_0)$ and $Poisson(\mu = E_{alt} = RR \times E_0)$: solve

$$Z_{\alpha/2} \times \{E_0\}^{1/2} + Z_\beta \times \{E_{alt}\}^{1/2} = E_{alt} - E_0.$$

POWER OF (1-sample) Poisson-based test of E_null versus E_alt

jh 2006.03.18

supply E_null, alpha level, E_alt

		n		**20**	**Rate**
		E_null		**4.5**	**Ratio**
		E_alt		**13.5**	**3.00**
2-sided		**alpha**		**0.050**	
					POWER
	y	<- # Events in the amount of Experience studie			**0.865**

↓ critical region

↓	y	Prob(y | E_null =4.5)	Prob(≥ y | E_null =4.5)	Prob(y | E_alt = 13.5)	Prob(≥ y | E_alt = 13.5)
	0	0.0111	1.0000	0.0000	
	1	0.0500	0.9889	0.0000	
	2	0.1125	0.9389	-0.0001	
	3	0.1687	0.8264	-0.0006	
	4	0.1898	0.6577	-0.0019	
	5	0.1708	0.4679	-0.0051	
	6	0.1281	0.2971	-0.0115	
	7	0.0824	0.1689	-0.0222	
	8	0.0463	0.0866	-0.0375	
	9	0.0232	0.0403	-0.0563	
*	10	0.0104	0.0171	-0.0760	0.865
*	11	0.0043	0.0067	-0.0932	
*	12	0.0016	0.0024	-0.1049	
*	13	0.0006	0.0008	-0.1089	
*	14	0.0002	0.0003	-0.1050	
*	15	0.0001	0.0001	-0.0945	
*	16	0.0000	0.0000	-0.0798	
*	17	0.0000	0.0000	-0.0633	
*	18	0.0000	0.0000	-0.0475	
*	19	0.0000	0.0000	-0.0337	
*	20	0.0000	0.0000	-0.0228	
*	21	0.0000	0.0000	-0.0146	
*	22	0.0000	0.0000	-0.0090	
*	23	0.0000	0.0000	-0.0053	
*	24	0.0000	0.0000	-0.0030	
*	25	0.0000	0.0000	-0.0016	

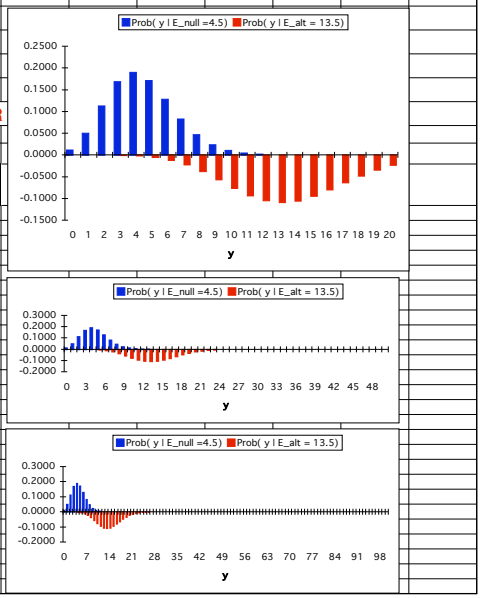

Figure 6: Using exact Poisson Probabilities [see 'Power for test of E = E_{null} vs E = E_{alt}: Excel worksheet' under Resources]

1−2α	0.95		0.9		0.8	
α	0.025		0.05		0.1	
count	Lower	Upper	Lower	Upper	Lower	Upper
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
25	16.18	36.90	17.38	34.92	18.84	32.71
26	16.98	38.10	18.22	36.08	19.72	33.84
27	17.79	39.28	19.06	37.23	20.59	34.96
28	18.61	40.47	19.90	38.39	21.47	36.08
29	19.42	41.65	20.75	39.54	22.35	37.20
30	20.24	42.83	21.59	40.69	23.23	38.32

Figure 7: (Exact) Confidence limits for the expectation [i.e. the μ parameter] of a Poisson random variable. Example: if observe 6 events in a certain amount of experience, then 95% CI for the mean count for this same amount of experience is (2.20, 13.06)

7 References

*Clayton D and Hill M. Statistical Models for Epidemiology Chs 4, 5, 12.2

*Walker A Observation and Inference, p13,107,154.

Armitage P Berry G & Matthews JNS [4th edition, 2002] Statistical Methods in Medical Research sections 3.7 , 5.3, 6.3.

Colton T Statistics in Medicine, pp 16-17 and 77-78.

Kahn HA, Sempos CT Statistical Methods in Epidemiology pp 218-219.

Selvin S Statistical Analysis of Epidemiologic Data Ch 5 (clustering) and Appendix B (Binomial/Poisson).

Miettinen O Theoretical Epidemiology p 295.

Breslow N, Day N Statistical Methods in Cancer ResearchVol II: Analysis of Cohort Studies pp68-70 (SMR) pp131-135; sect. 7.2 (power/sample size) Statistical Methods in Cancer ResearchVol I: Analysis of Case-Control Studies p134 (test-based CI's).

Rothman K, Greenland S [1998] Modern Epidemiology pp 234- pp404-5 (overdispersion) 570-571 (Poisson regression).

Rothman K, Boice J Epidemiologic Analysis on a Programmable Calculator.

Rothman K [1986] Modern Epidemiology.

Rothman K [2002] Introduction to Epidemiology pp 133-4 & 137-139

POISSON, Siméon Denis 1781-1840

from...
`http://www.york.ac.uk/depts/maths/histstat/people/sources.htm`

See also...

`http://www.encyclopedia.com/topic/Simeon_Denis_Poisson.aspx`

`http://en.wikipedia.org/wiki/Poisson_distribution`

0 Exercises

0.1 (m-s) Working with logs of counts and logs of rates

In order to have a sampling distribution that is closer to Gaussian – sample counts, and ratios of them tend to have nasty sampling distributions –we often transform from the $(0, \infty)$ scale for a count y and its expectation, μ, to the $(-\infty, \infty)$ $\log[y]$ and $\log[\mu]$ scale.

Thus, we do all our inference (SE calculations, CI's, tests) on the log scale, then transform back to the count or rate (or if comparative, rate ratio) scale.

1. Suppose $Y \sim$ Poisson(μ) with associated rate estimate $\hat{\lambda} = Y/PT$[19]. Derive the variances for the random variables $\log[Y]$ and $\log[\hat{\lambda}]$. Ignore the possibility of obtaining $\hat{\mu} = 0$ i.e., $\hat{\lambda} = 0/PT = 0$.
2. What is the variance for the log of a rate ratio, i.e., $\log[\hat{\lambda}_2 \div \hat{\lambda}_1]$?

0.2 (m-s) The Poisson Family as a 'Closed under Addition' Family

Show that if $Y_1 \sim Poisson(\mu_1)$ and $Y_2 \sim Poisson(\mu_2)$ are independent random variables, then $Y = Y_1 + Y_2 \sim Poisson(\mu_1 + \mu_2)$.

0.3 (m-s) Link between Poisson and Exponential Distributions

Show that if the random times $T_1, T_2, \ldots$ between successive events can be regarded as i.i.d observations from an exponential distribution with mean μ_T, then the number Y of events in a fixed time-window of length W has a Poisson Distribution with mean or expectation $\mu_Y = W \times \lambda = W \times (1/\mu_T)$.

0.4 (m-s) Link between tail areas of Poisson and χ^2 Distributions

In section 5 of Fisher 1935, he states that 'it will be noticed' (from section 4) that, when its number of degrees n is even, the probability of the variate $\frac{1}{2}\chi^2$

[19] PT = amount of Population Time

exceeding any specified value μ is

$$e^{-\mu}\{1+\mu+\mu^2/2!+\cdots+\mu^{(n-2)/2}/[(n-2)/2]!\}.$$

From this, with $Y \sim Poisson[\mu]$, and $n = 2y$, derive a way to obtain $Prob[Y \geq y \mid \mu]$ from the cdf function of the χ^2 Distribution. From this, derive a way to obtain, from a single Poisson count y, the exact lower $\alpha/2$ and upper $\alpha/2$ limits for the mean of the Poisson Distribution it arose from. The article in Accromαth illustrates this link, using a diagram we adapted from the tire-ruptures example.

0.5 (m-s) The Fisher information that a Poisson random variable carries about its expectation and about the log of this expectation

(Wikipedia) "The Fisher information is the amount of information that an observable random variable Y carries about an unknown parameter θ upon which the likelihood function of θ, $L(\mu) = f(Y;\theta)$, depends." The Fisher Information is defined as

$$I(\theta) = E\left\{\left[\frac{d}{d\theta}\ln f(Y;\theta)\right]^2\Big|_\theta\right\}.$$

As per Casella and Berger, 2nd Ed. p338, in an exponential family we also have that

$$E\left\{\left[\frac{d}{d\theta}\ln f(Y;\theta)\right]^2\Big|_\theta\right\} = -E\left\{\frac{d^2}{d\theta^2}\ln f(Y;\theta)\Big|_\theta\right\}.$$

1. Calculate the Fisher Information about the parameter μ in the case of the random variable $Y \sim Poisson(\mu)$, with

$$L(\mu) = f(Y;\mu) = \exp[-\mu]\times\mu^Y/Y!$$

2. Calculate the Fisher Information about the parameter $\theta = \log(\mu)$.

0.6 (m-s) The Poisson distribution as an approximation to the binomial distribution

Stigler, in The American Statistician, February 2013 (see Resources), writes

"The Poisson distribution is often introduced as an approximation to the binomial distribution, an approximation that improves in accuracy as n, the number of binomial trials, increases, while np, the expected value, does not:

$$\frac{e^{-np}(np)^k}{k!} \cong \binom{n}{k}p^k(1-p)^{n-k}$$

The presentation is usually accompanied by a proof that invokes some version of the approximation $(1-1/n)^{-n} \cong e = 2.71828\ldots$. Poisson's own derivation proceeded in much the same manner (Poisson 1837, p. 206; Stigler 1982a), as did a bestselling textbook published in 1936 by Hyman Levy and Leonard Roth. Those authors were, respectively, professor of Mathematics and assistant lecturer in Mathematics at Imperial College London. Figure 1 reproduces the relevant passage from Levy and Roth (1936).

to b is $1-1/n$. If we now consider the sample t, containing nt/T elements, the probability that none of them belongs to b is

$$\left(1-\frac{1}{n}\right)\left(1-\frac{1}{n}\right)\ldots\left(1-\frac{1}{n}\right)\ldots \text{ to } \frac{nt}{T} \text{ factors} = \left(1-\frac{1}{n}\right)^{nt/T},$$

$$= \left(1-\frac{1}{n}\right)^{-n(-t/T)}.$$

If n is sufficiently large,† $\left(1-\frac{1}{n}\right)^{-n}$ is approximately e, where

$$e = 1+\frac{1}{1!}+\frac{1}{2!}+\ldots = 2{\cdot}71828\ldots.$$

Hence the required probability is approximately $e^{-t/T}$.

† For example, if $n = 10$, the error in replacing $\left(1-\frac{1}{n}\right)^{-n}$ by e does not affect the sixth decimal place.

Figure 1. Part of page 80 of Levy and Roth (1936), showing the approximation and the footnote.

For many years, I have been presenting my class with a copy of this page from Levy and Roth and asking them, as a homework exercise, to answer a simple question: **Is the footnote correct?** "

1. ***BIOS601 Exercise***: Answer Stigler's question.

0.7 CI's for the incidence of percutaneous injuries in the various types of residencies

The NEJM authors did not say how they got the CIs for the Rates per Intern-Month, shown in Table 1 on page 6. The CI for the overall rate closely matches the large-sample one that JH has in his Notes. Apply the exact method to obtain CI's for the 3 'P's', Pediatrics, Psychiatry and Pathology, where the observed numerators are all under 30. [Table on p. 10 may help]

0.8 Comparison of various CI's for the expectation, μ of a Poisson random variable, on the basis of a single count y

Fill in the blanks in the table below, and compare the accuracy of different approximations to the exact 95% CI for μ, based on a count of y.

Observe $y =$	3*	6	15	33**	78***	100
Exact CI:	?	?	?	?	?	?
Approximation						
Wilson-Hilferty	?	?	?	?	?	?
1st principles, y	?	?	?	?	?	?
1st principles, $y^{1/2}$	?	?	?	?	?	?
SE-based, y	?	?	?	?	?	?
SE-based, $\log(y)$	?	?	?	?	?	?

* Rothman 2002 p134: 3 cases in 2500 PY. ** No. of lung cancer deaths in women aged 55-60 in Quebec in 1971. ***Total number of cancers in concerned area in Alberta SourGas study.

0.9 Power Calculations

A researcher wishes to compare the numbers of new cases of a particular disease in the 'PT' Population-Time units exposed to a potentially noxious agent with the $E_0 = \mu_0 = 15.6$ that would be expected in this amount of Population Time if rates (already observed) in a LARGE unexposed experience prevailed. The researcher will use a 1-sided test with $\alpha = 0.05$ to test H_0 : $\mu_{\text{in this amount of exposed PT}} = 15.6$ vs. H_{alt} : $\mu_{\text{in this amount of exposed PT}} > 15.6$.

The amount of PT is fixed. Thus there is no point in the researcher calculating *what amount of PT would be required* so that, if $\mu_{exposed} =$ (say) $2 \times \mu_{un-exposed}$, there would be an 80% chance of obtaining a statistically significant elevation (i.e., an experience large enough to have 80% power to 'detect' a doubling of the incidence rate). Instead, the researcher decided to calculate the *power*, with the given fixed amount of PT that can be studied, to 'detect' a doubling or a tripling of the incidence rate.

Perform this power calculation. You may find it easier (and more transparent) to work with the exact Poisson probabilities (e.g. in a spreadsheet or in `R`).

0.10 Perfect Results ?

The following excerpt is from the Vaccine Arm of Table 3 of an Article in the NEJM in 2002[20]. We will look at the comparison with the Placebo arm when we get to comparative studies.

Efficacy Analyses of a Human Papillomavirus Type 16 L1 Virus-like-particle Vaccine.

	End point	HPV-16 VACCINE GROUP			
Efficacy Analysis	Type of HPV-16 Infection	No. of Women	Cases Of Infection	Woman-Yr At Risk	Rate per 100 Woman-Yr At Risk
(1)*	P.	768	0	1084.0	0
(2)**	P.	800	0	1128.0	0
(3)*	P. or T.	768	6	1084.0	0.6

(1) Primary per-protocol

(2) Including women with general protocol violations

(3) Secondary per-protocol

P = Persistent; T=transient

*The per-protocol population included women who received the full regimen of study vaccine and who were seronegative for HPV-16 and negative for HPV-16 DNA on day 0 and negative for HPV-16 DNA at month 7 and in any biopsy specimens obtained between day 0 and month 7; who did not engage in sexual intercourse within 48 hours before the day 0 or month 7 visit; who did not receive any nonstudy vaccine within specified time limits relative to vaccination; who did not receive courses of certain oral or parenteral immunosuppressive agents, immune globulin, or blood products; who were not enrolled in another study of an investigational agent; and who had a month

[20] The New England Journal of Medicine Vol 347 Nov 21, 2002, p1645 A Controlled trail of a Human Papillomavirus Type 16 Vaccine. Laura A. Koutsky et al., for The Proof of Principle Study Investigators.

7 visit within the range considered acceptable for determining the month 7 HPV-16 status.

**The population includes women who received the full regimen of study vaccine and who were seronegative for HPV-16 and negative for HPV-16 DNA on day 0 and negative for HPV-16 DNA at month 7 and in any biopsy specimens obtained between day 0 and month 7.

Questions

1. In their Statistical Methods, the authors state: "The study employed a fixed-number-of-events design. At least 31 cases of persistent HPV-16 infection were required for the study to show a statistically significant reduction in the primary end point (assuming that the true vaccine efficacy was at least 75 percent with a power of at least 90 percent). Accounting for dropouts and women who were HPV-16-positive at enrollment and assuming an event rate of approximately 2 percent per year, we estimated that approximately 2350 women had to be enrolled to yield at least 31 cases of HPV-16 infection. Although the study will continue until all women complete four years of follow-up, the primary analysis was initiated on August 31, 2001, as soon as at least 31 cases were known to have occurred. Thus, the primary analysis includes all safety and efficacy data from visits that occurred on or before that date."

   Why did the authors use a 'fixed-number-of-events' rather than 'fixed number of subjects for a fixed amount of time' design?

2. Calculate 95% 2-sided CIs to accompany the 3 point estimates of infection rate.

0.11 With luck, will the Royal Mint have enough coins?

Refer to the story "Babies who share royal birthday will coin it" [21] and to the average of 1,983 births a day.

1. (From the information in the article) what is the probability that the Mint will have enough, if they mint 2,013 coins? State any assumptions made.

2. How many should they mint to be 99.99% sure of having enough?

3. The average number of births per day varies slightly by season, and substantially by day of the week – JH could not find day-of-week data for the UK[22], but did find 2010 data from the USA.[23] Rework questions 1 and 2 using a worst case scenario, and assuming the same day-of-week patterns seen in the USA apply in England and Wales [***scale row 1 of the CDC table for the USA down to match the size of UK***]

4. For shorthand purposes, refer to the probability of having enough coins as the '*non-exceedance*' probability.[24] How close is the mean of the 7 non-exceedance probabilities to the non-exceedance probability calculated at the mean no. of births per day? How close is the *median* non-exceedance probability? What if we switched focus to the *exceedance* probability rather than the non-exceedance probability?

5. (Again, under your worst case scenario) how many pink and blue pouches would you recommend they have ready?

[21] Seems that 'to coin it' means means 'to profit'

[22] http://www.statistics.gov.uk/hub/population/births-and-fertility/live-births-and-stillbirths

[23] http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm

[24] A New Zealand webpage entitled What does Annual Exceedance Probability or AEP mean? says 'This term is generally referred to in rules that regulate discharges of contaminants including stormwater, wastewater, greywater. It can also be referred to in rules that regulate the use of land that may result in a discharge including offal pits, storage facilities for animal effluent, stockpiling organic matter (including composting) and storage of hazardous substances.
The Annual Exceedance Probability is the chance or probability of a natural hazard event (usually a rainfall or flooding event) occurring annually and is usually expressed as a percentage. Bigger rainfall events occur (are exceeded) less often and will therefore have a lesser annual probability.
Example 1: 2% exceedance probability rainfall event: A 2% Annual Exceedance Probability rainfall event has a 2% chance of occurring in a year, so once in every 50 years.
Example 2: 20% exceedance probability rainfall event: A 20% Annual Exceedance Probability rainfall event has a 20% chance of occurring in a year, so once in every 5 years.

No SIM 6:48 AM 100%

THE TIMES
Friday, 5 July 2013

News

Babies who share royal birthday will coin it

Valentine Low

Babies born on the same day as the Duke and Duchess of Cambridge's first child are to receive a commemorative silver penny, the Royal Mint announced yesterday.

It is giving away 2,013 of the pennies, which reflect the tradition of marking a new birth with a gift of silver for good luck. This, however, is a new tradition: it will be the first time the Royal Mint has marked a royal birth by giving away coins.

The Royal Mint will give away 2,013 of the silver pennies in special pouches
PA

The pennies are worth £28 each, making the overall cost to the state-owned company more than £50,000.

The silver penny, which will be presented in a pink or blue pouch, is marked with the year 2013 to commemorate the baby girl or boy's year of birth and features a shield of the Royal Arms designed by Matthew Dent.

Shane Bissett, Director of Commemorative Coin at the Royal Mint, said: "The birth of the royal baby will be a joyous occasion, not just for Their Royal Highnesses the Duke and Duchess of Cambridge, but also for the whole nation, as we prepare to celebrate another remarkable milestone in their life journey together.

"However, it will also be a special day for many mothers and fathers across the country as they, too, welcome the arrival of their new baby; hence why we wanted to extend this historical moment to them with a lucky silver penny."

Parents of babies born on the same day as the royal baby have 60 days to claim their silver penny by visiting Facebook.com/theroyalmint to register the birth of their child. With luck, the Royal Mint should have enough coins: an average of 1,983 babies are born in England and Wales each day. ■

CONTENTS EDITION LIVE NEWS

Beyond 20/20 WDS - Table view - ME_ROUT by DOB_WK (2010 Birth Data - State Detail)

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National Vital Statistics System
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

Tables | Table | Chart

ME_ROUT by DOB_WK (2010 Birth Data - State Detail)

Other:

DOB_WK / ME_ROUT	Total	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Total	3,999,386	369,704	606,424	666,686	656,694	649,636	633,899	416,343
Vaginal-Spontaneous	1,931,624	203,437	280,188	310,516	309,225	306,652	295,023	226,583
Vaginal-Forceps	20,868	2,069	3,055	3,456	3,506	3,352	3,056	2,374
Vaginal-Vacuum	89,879	9,114	12,669	14,962	14,761	14,358	13,566	10,449
Cesarean	995,945	67,410	163,540	176,929	170,666	168,245	170,456	78,699
Not stated	17,568	1,574	2,682	3,022	2,964	2,793	2,730	1,803
Not on certificate	943,502	86,100	144,290	157,801	155,572	154,236	149,068	96,435

DayOfWeek	Total	January	February	March	April	May	June	July	August	September	October	November	December
Total	3999386	323249	301994	338613	325028	328273	334535	345199	349747	350745	336809	326220	338974
Sunday	369704	34516	27851	27331	27326	34675	28456	29104	36658	30460	36798	28536	27993
Monday	606424	45873	45899	57699	46839	54815	47351	44502	61073	45406	47795	60967	48205
Tuesday	666686	50373	49751	62979	50302	51071	63178	51325	65572	53189	51056	65209	52681
Wednesday	656694	49042	49277	62067	49237	50024	63541	52202	51530	67103	49698	49109	63864
Thursday	649636	49448	49230	48981	61017	49637	50787	64681	51511	67279	49963	45162	61940
Friday	633899	55630	48382	48155	59075	48472	48887	62232	49800	52728	61238	45280	54020
Saturday	416343	38367	31604	31401	31232	39579	32335	41153	33603	34580	40261	31957	30271

See article, by a student and teacher of `bios601`, on this topic
`https://www.significancemagazine.com/585` and

Mystery Data quiz, in Significance Magazine, also on the timing of births.
`https://rss-onlinelibrary-wiley-com.proxy3.library.mcgill.ca/doi/full/10.1111/j.1740-9713.2017.01026.x`
or `http://www.medicine.mcgill.ca/epidemiology/hanley/mysteryData/`

0.12 2 (indep.) Poisson r.v.'s → 1 Binomial distribution

Suppose we wish to compare 2 event-rates, λ_1 in 'exposed' (1) person time and λ_0 in 'unexposed' (0) person time. Denote the (to-be-observed) numbers of events in Y_1 and Y_0 person-years by D_1 and D_0 respectively.[25]

Then

$$D_1 \sim \text{Poisson}(\mu_1) \text{ and } D_0 \sim \text{Poisson}(\mu_0),$$

where

$$\mu_1 = \lambda_1 \times Y_1 \text{ and } \mu_0 = \lambda_0 \times Y_0.$$

Show that by conditioning on (fixing) the sum $D = D_1 + D_0$, we obtain a binomial random variable:

$$(D_1 \mid D) \sim Binomial\left(D,\ \pi = \frac{\mu_1}{\mu_1 + \mu_0} = \frac{\lambda_1 Y_1}{\lambda_0 Y_0 + \lambda_1 Y_1} = \frac{\theta Y_1}{Y_0 + \theta Y_1}\right),$$

where θ is the Rate Ratio λ_1/λ_0,

and that

$$\Omega = \frac{\pi}{1-\pi} = \frac{E[D_1]}{E[D_0]} = \frac{Y_1}{Y_0} \times \frac{\lambda_1}{\lambda_0}.$$

0.13 Cancer screening trials: sample size/data-analysis

[new in 2017, and a prelude to the visit of Steven Skates (UK Ovarian Cancer Screening Trial) on Oct 3, 2017]

The following sections are taken from 'Biometric design of the Mayo Lung Project for early detection and localization of bronchogenic carcinoma.' Taylor WF, Fontana RS. Cancer. 1972 Nov;30(5):1344-7.

ABSTRACT

Several important aspects of the Mayo Lung Project demand evaluation. These are: 1. Acceptance. Will people accept such a screening program? 2. Case finding. Does the screen pick out the people most likely to have or develop bronchogenic carcinoma? 3. Effectiveness. If an early case of bronchogenic carcinoma is found, will prompt treatment extend life beyond the time at which death from this disease would have occurred if treatment had been delayed? Direct measurement of effectiveness is not possible, and indirect methods must be used. A group of patients, all of whom are considered suitable for the screening program, are being divided randomly into two subgroups, one to be screened and the other to be kept as an unscreened control. Mortality in the two groups is to be compared for 5 years, and hopefully for 10 years. We also consider here sample size requirements and reports on some of the characteristics of the first 500 patients.

DESIGN OF PROJECT

Subjects and methods: In the course of usual procedure at the Mayo Clinic, we identify each male patient who is 45 years of age or older and who smokes :it least one pack of cigarettes a day. As part of the routine health examination of such patients, a standard 14 by 17-inch posterior-anterior chest roentgenogram is made and studied and a pooled 3-day "deep cough" sputum specimen is examined cytologically. We have the patients answer a Lung-Health Questionnaire as part of this project. All men found free from clinical evidence of lung cancer and free from other serious diseases (to the degree that life expectancy is estimated as at least 5 years) are included in this study. These patients are assigned at random to one of two groups.

1. One group, designated *controls*, receives care and advice of the standard which is current practice at Mayo Clinic. This includes the recommendation of the Clinic's Division of Thoracic Diseases that a chest roentgenogram and a sputum cytology test be obtained at least once a year and that the patient stop smoking. However, these men will be told nothing of the screening program. Rather, they will be examined and will receive care at their own request as if no screening program existed. A routine follow-up communication will be made with each man at least once a year for at least 10 years to determine survival status. If a man dies, his death certificate will be obtained and the circumstances of his death will be determined from his local doctor.

2. The other group, called *participants*, will be treated initially just as the first group, but these men will also be urged to participate in the intensive bronchogenic carcinoma screening project.[26] Men who refuse will not be dropped; they will be followed as closely as possible through correspondence and will be included when comparisons are made with the first group.

Analysis: If the work is carefully clone and if adequate time is allotted for the project, a moderate difference in observed lung cancer mortality can be deemed significant statistically and can be attributed to some aspect and

[25] Clayton and Hills used the letter D, since it is short for numbers of 'deaths'; not all of the events in epidemiology are terminal, or unwanted.

[26] "We decided to use a 4-month screening interval because previous studies suggested that longer intervals were too long. We thought a 4-month interval would be acceptable to our patients and achievable by our technical personnel."

effect of the screening procedure. (We may not know which aspect, but at least we will have established that screening and early treatment have some effect, and we will have incentive to pursue the matter further. Such aspects as how intensive the screening should be or how costs can be reduced are perhaps better delayed until the question of gross effectiveness is answered.)

Notice that we *will not merely compare survival time of early-discovered and late-discovered cases*. There is an unknown bias in favor of early-discovered cases, even if no treatment is employed. *Notice also that we do not rely on volunteers for one group and let the comparison group consist of nonvolunteers*. Instead, we divide the group of eligible people at random into two groups, offer the screening to one of them, and then compare the two groups in their entirety. Finally, it should be noted that we do not plan to make a comparison of the incidence of cancer or the survival of cancer patients among the unscreened controls with that of the participants, because to get such detailed information we would have to communicate with the control patients and thus lose part of the difference between control and screened patients. The screened group may have a higher observed incidence because we observe them more closely. We want the two groups to be observed with different intensity-within the bounds of currently acceptable medical practice-because this is what the study is all about.

A word about eligibility: An early benefit from this work results from the first screening. The cases of lung cancer found then will be interesting in themselves and will be worked up thoroughly. The initial screening should also eliminate from further study patients who for other reasons are considered to have an unusually short expectation of life. This, of course, will be somewhat subjective, but decisions will be made as consistently as possible, in accord with written guidelines.

Sample size and time required: We have considered sample size in relation to comparison of mortality from bronchogenic carcinoma in the two designated groups. Suppose we admit N men into each group. After 5 years there will have occurred T_1 and T_2 man-years of exposure in each group, and D_1 and D_2 deaths. If $T_1 \cong T_2$, as is likely, we merely must determine whether the control deaths D_1, exceed significantly the screened deaths D_2. **It is reasonable to consider the D_1 and D_2 deaths as independent binomial trials.** Let p denote the probability that, **given a death occurs**, it occurs in the controls. Let H_0 be the hypothesis $p = 1/2$, and let H_1 be the alternative of interest, $p = 2/3$. (*This corresponds to reducing the lung cancer death rate in the screened group to half that in the controls.*) We want the following two conditions to be met,

$$P(\text{reject } H_0 \text{ in favor of } H_1 | H_0 \text{ true}) = \alpha = 0.05$$

$$P(\text{reject } H_0 \text{ in favor of } H_1 | H_1 \text{ true}) = \beta = 0.95.$$

We reject H_0 in favor of H_1 whenever

$$\left[\left(\frac{D_1}{D_1 + D_2} - \frac{1}{2} \right) \Big/ \sqrt{\frac{1}{4} \frac{1}{D_1 + D_2}} \right] \geq 1.645.$$

The probability that this occurs under H_0 is about 0.05. The probability under H_1 is about 0.95 if $D_1 + D_2 = 90$.

Now the question is: how how many men must we examine for how long to get about 90 deaths from bronchogenic carcinoma? (The following information is in the nature of a first attempt to estimate this quantity.) Suppose we wish to get an answer in 5 years, and assume from published data and some educated guessing that 5 deaths per 1,000 man-years will occur among the controls and 2.5 deaths per 1,000 man-years among the participants in the close surveillance. We expect to have 60 deaths among the controls and 30 among the participants if we observe 12,000 man-years in each. These estimates, based on averages, do not take into account chance variation. If we wish to be 95% sure of obtaining 60 and 30 deaths, respectively, we need to observe 12,000 man-years in each group. We think we can obtain such numbers from our present case load but not without difficulty. Initial plans calling for a total of 6,000 men (3,000 in each group) may have to be modified and will be as soon as deemed essential. We anticipate some losses; there may well be men who refuse to continue under screening These are not to be entirely lost; their cases will be followed anyway by mail. But it does dilute the difference between the qroups and makes the true effects of screening more difficult to detect. The surveillance effort will have to be vigorous and encouraging.

Will 5 years be long enough, even with the numbers of subjects proposed? Perhaps not; but regardless of the early outcome and regardless of whether the actual screening goes on beyond 5 years, these men should continue to be traced for at least a total of 10 years. In our opinion, important information about survival following early treatment will require more than 5 years' study. This opinion is based on possible recurrence of the initial cancer, as well as concern over development of an entirely new primary cancer, particularly in individuals with squamous cell carcinoma.

— — —

Questions - for `bios601` exercise

1. re-write the sentence "It is reasonable to consider the D_1 and D_2 deaths as independent binomial trials."

2. With $D = 90$ and (the null) $p = 0.5$, use the `pbinom` function to calculate $d_1^{critical}$, the smallest d_1 such that $\text{Prob}[D_1 \geq d_1] \; < \; \alpha$. [see Note[27]]

3. (Staying with $D = 90$) use the non-null $p = 2/3$ in the `pbinom` function to calculate $\text{Prob}[D_1 \geq d_1^{critical}]$ and check the value against the 'about 95%' [power] given by Taylor and Fontana.

   JH finds that rough diagrams are a big help in setting up power calculations like these.

4. Comment on their use of the letter β to denote this probability.

5. Taylor and Fontana did not have easy access to binomial calculations, so they used a Normal approximation to the binomial. i.e,

$$(D_1|D) \sim N[\; \mu = D \times p, \; \text{Var} \; = D \times p \times (1-p) \;].$$

   (Staying with $D = 90$) use this approximation to repeat the above calculations for $p = 1/2$ and $p = 2/3$.

6. In the above H_1 the alternative of interest, $p = 2/3$, corresponded to reducing the lung cancer death rate in the screened group to half that in the controls, i.e. (using their '1' to denote to denote the controls, and '2' to denote the participants) to a situation where $\lambda_2 = 0.5 \times \lambda_1$.

   But what if this alternative is **too optimistic**? Consider four more modest scenarios: $H_2 : \lambda_2 = 0.6 \times \lambda_1$; $H_3 : \lambda_2 = 0.7 \times \lambda_1$; $H_4 : \lambda_2 = 0.8 \times \lambda_1$; and $H_5 : \lambda_2 = 0.9 \times \lambda_1$, i.e., reductions of 40%, 30%, 20%, and 10% respectively. First, convert these 4 scenarios to the corresponding 4 non-null values of p and (staying with $D = 90$), calculate $\text{Prob}[D_1 \geq d_1^{critical}]$, i.e., the statistical power, for each of these.[28]

7. As you will have found, the power against H_4 (a 20% reduction) is low when D is just 90. By trial and error, or directly, calculate the D one would need to have 80% power (rather than their 95%) but against just a 20% reduction.

   Convert this required D to a required number of man-years, using a mortality rate of 3 per 1,000 man-years in the controls.[29]

[27] Note the values of `pbinom(3,4,.5)` and `pbinom(3,4,.5,lower.tail=FALSE)`

[28] Use exact binomials, or normal approximations, as you wish.

[29] This rate of 3/1,000 MY was calculated 'after-the-fact' in 1986, after 115 lung cancer deaths had been observed in 4,600 men followed for an average of just over 8 years. As you will have seen above, the rate used for planning purposes was 5 per 1,000 man-years.

AFTERMATH 1981, 1986, 2000 || CT screening: 2006, 2011

Some Results of Screening for Early Lung Cancer

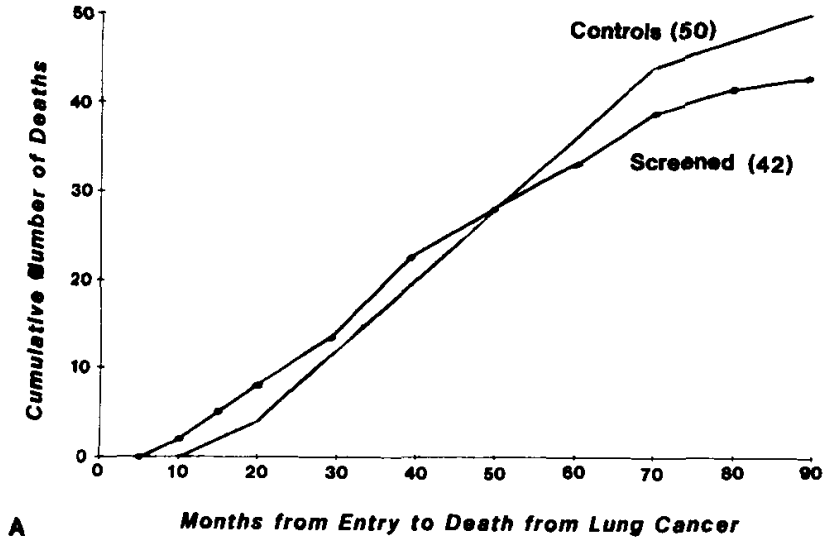
WILLIAM F. TAYLOR, PHD, ROBERT S. FONTANA, MD, MARY ANN UHLENHOPP, BA, AND CHARLES S. DAVIS, MS

Screening for lung cancer is somewhat controversial in that very few evaluations of the screening process have been made, and even fewer have involved the use of concomitant, unscreened controls. This report of the Mayo Lung Project provides evaluation of a randomly selected 4500 clinic patients, offered screening for lung cancer at four-month intervals for six years. Another 4500 randomly selected controls not offered screening were merely observed. Good screening is defined, the Mayo project is evaluated, and puzzling results are presented and discussed.

From the screened group, 98 new cases of lung cancer have been detected, 67 by study screening and 31 by spontaneous reporting of symptoms (15) or by x-ray examinations (16) done in other than study circumstances. From the controls, 64 new lung cancer cases have been detected, 43 by symptoms and 21 by other methods. Lung cancer mortality is 39 for study patients and 41 for controls. There is thus no evidence at this time that early case finding has decreased mortality from lung cancer.

***Cancer* 47:1114–1120, 1981.**

JH is puzzled by the sentence 'Lung cancer mortality is 39 for study patients and 41 for controls.' in the above summary. The 39 and 41 do not agree with the numbers (42 and 50) given elsewhere in the text and in the various Figures.



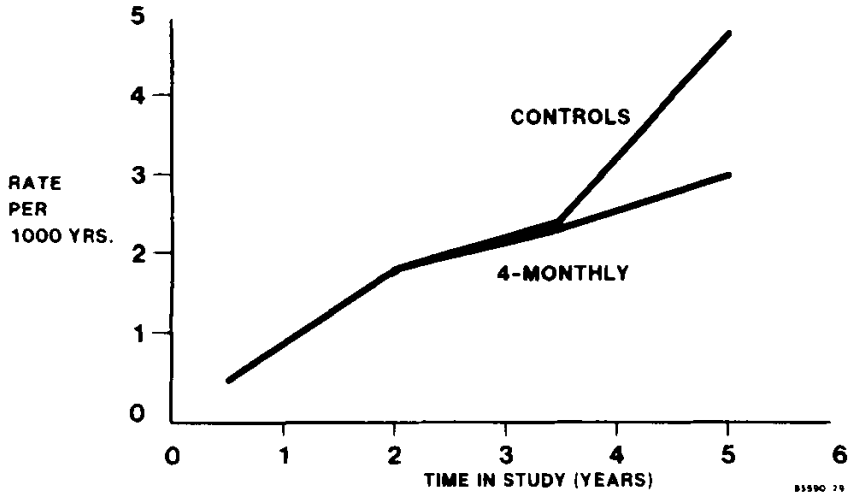


FIG. 7. Lung cancer death rates by time in study—control and screened patients.

[From Discussion] 'A second hopeful observation has to do with the actual lung cancer death rates for controls and screened patients, as shown in Figure 7. Attention is directed particularly to the rates for those patients who have been in the study four years or more. The death rate from lung cancer for the controls exceeds that of the screened group by a considerable amount, although this is not yet statistically significant either. However, this trend has been observed for the last three years, and the difference is growing.

We believe that lung cancer screening appears promising for squamous cancers and for adeno-carcinomas but not for small or large cell un-differentiated tumors. Our recommendation now is to continue observation well into the follow-up phase (at least three to five more years). We suggest that no lung cancer screening projects be established for the general population of older male smokers at this time. But, we also suggest that we do not now know enough about this matter to make definitive statements.

Lung Cancer Screening: The Mayo Program [1986]

Robert S. Fontana, MD; David R. Sanderson, MD; Lewis B. Woolner, MD; William F. Taylor, PhD; W. Eugene Miller, MD; and John R. Muhm, MD

Journal of Occupational Medicine/Volume 28 No. 8/August 1986

(Summary) The National Cancer Institute has sponsored three randomized controlled trials of screening for early lung cancer in large, high-risk populations to determine whether (1) lung cancer detection can be improved by adding sputum cytological screening every 4 months to chest roentgenography done either yearly or every 4 months; and (2) lung cancer mortality can be significantly reduced by this type of screening program, followed by appropriate treatment. Results of the three trials suggest that (1) sputum cytology alone detects 15% to 20% of lung cancers, almost all of which are squamous cancers with a favorable prognosis; and (2) chest roentgenography may be a more effective test for early-stage lung cancer than previous reports have suggested. Nevertheless, results of the randomized trial conducted at the Mayo Clinic showed that offering both procedures to high-risk outpatients every 4 months conferred no mortality advantage over standard medical practice that included recommended annual testing.

(From results section) In the MLP randomized trial, the death rates from all causes (per 1,000 person-years) were high: 24.8% in the screened every 4 months and 24.6% in the control group. The major competing death risk was ischemic cardiovascular disease.

There were 122 lung cancer deaths in the group screened every 4 months and 115 in the control group. Seven deaths in the group screened every 4 months and six deaths in the control group were attributed to surgery for lung cancer. These were treated as lung cancer deaths.

The death rate from lung cancer was 3.2/1,000 person-years in the group screened every 4 months and 3.0 among the control subjects. Like the cumulative numbers of unresectable cancers, the cumulative numbers of lung cancer deaths in the two groups were comparable, both during and after the period of active screening.

Comments

The results of the MLP randomized controlled trial do not justify recommending large-scale programs of radiological or cytological screening for lung cancer. Such programs are usually initiated by those who conduct them and should benefit the participants by reducing lung cancer mortality.' The MLP trial did not demonstrate this sort of benefit.

Neither do the results of the MLP mean that testing high-risk patients for

lung cancer by chest x-ray film or sputum cytology is not useful, as some have claimed.' All who participated in the MLP trial received an initial (prevalence) radiological and cytological screening. The randomized trial simply shows that offering the two procedures every 4 months to high-risk Mayo outpatients who have had one negative screening confers no morality [*sic*][30] advantage over routine Mayo Clinic practice with a recommendation of annual testing. The randomized, controlled trials conducted at the Johns Hopkins Medical Institutions and at the Memorial Sloan-Kettering Cancer Center offered all participants annual chest roentgenograms. In addition, half of the men in each of these trials were randomly allocated to a group offered sputum cytology every 4 months. Results from both trials indicate that in the populations screened by x-ray film only, as well as in the populations screened by x-ray film and cytology, the proportion of early-stage, resectable lung cancers and the lung cancer survivorship have been substantially better than those observed in previously reported lung cancer screening programs. However, like the MLP, no significant difference in lung cancer mortality has been observed between the two populations in either the Hopkins or the Memorial trial.'

It should be emphasized that when the NCI randomized controlled trials commenced, it was generally accepted that yearly chest roentgenograms would not reduce lung cancer mortality. It was also believed that a large proportion of lung cancers would be detected cytologically, and the trials were designed with this in mind. Yet in all three screening programs, the great majority of lung cancers have been detected radiologically. Furthermore, sizable numbers were detected by nonstudy chest x-ray films in the control group of the MLP and by annual chest x-ray films in the control populations of the other two trials. It would be of interest to know what might have happened in these cases if chest roentgenograms had not been available to the control subjects.

The randomized controlled trial is ideal for assessing new procedures such as mammography, or new application of procedures such as screening populations at high risk of lung cancer by sputum cytology. Unfortunately, once a procedure has become an established part of medical practice, as the chest roentgenogram has (more than 80 million are taken year in the United States), it may become necessary to resort to other, less precise methods of evaluation, such as case-control studies.

Summary

Three large, long-term randomized controlled trials of screening for early-stage lung cancer by periodic chest x-ray film and sputum cytology have been conducted under the auspices of the National Cancer Institute. Cytological screening alone has detected only a small proportion of the lung cancers in these programs, although cytologically detected lung cancers tend to have a very favorable prognosis. Modern chest roentgenography appears to be a better method of detecting early-stage, resectable lung cancer than previous stud- ies have indicated.

Everyone who participated in the Mayo Clinic randomized trial had a satisfactory and negative initial (prevalence) radiological and cytological screening. The study group was then offered re-screening every 4 months, while the control group was offered standard medical care and advised to have annual chest radiography and sputum cytology.

The Mayo trial has shown significantly increased lung cancer detection, resectability, and survivorship in the study group compared with that of the control groups. Yet the death rates from lung cancer and from all causes have been almost identical in the two groups.

2000

Lung Cancer Mortality in the Mayo Lung Project: Impact of Extended Follow-up Pamela M. Marcus, Erik J. Bergstralh, Richard M. Fagerstrom, David E. Williams, Robert Fontana, William F. Taylor, Philip C. Prorok. [JNCI]

Background: The Mayo Lung Project (MLP) was a randomized, controlled clinical trial of lung cancer screening that was conducted in 9211 male smokers between 1971 and 1983. The intervention arm was offered chest x-ray and sputum cytology every 4 months for 6 years; the usual-care arm was advised at trial entry to receive the same tests annually. No lung cancer mortality benefit was evident at the end of the study. We have extended follow-up through 1996.

Methods: A National Death Index-PLUS search was used to assign vital status and date and cause of death for 6523 participants with unknown information. The median survival for lung cancer patients diagnosed before July 1, 1983, was calculated by use of Kaplan-Meier estimates. Survival curves were compared with the log-rank test.

Results: The median follow- up time was 20.5 years. Lung cancer mortality was 4.4 (95% confidence interval [CI] = 3.9-4.9) deaths per 1000 person-years in the intervention arm and 3.9 (95% CI = 3.5-4.4) in the usual-care arm (two-sided P for difference = .09). For participants diagnosed with lung cancer before July 1, 1983, survival was better in the intervention arm (two-sided P = .0039). The median survival for patients with resected early-stage disease was 16.0 years in the intervention arm versus 5.0 years in the usual-care arm.

Conclusions: Extended follow-up of MLP participants did not reveal a lung cancer mortality reduction for the intervention arm. Similar mortality but

[30] `https://en.wikipedia.org/wiki/Sic`

better survival for individuals in the intervention arm indicates that some lesions with limited clinical relevance may have been identified in the intervention arm. [J Natl Cancer Inst 2000;92:1308-16]

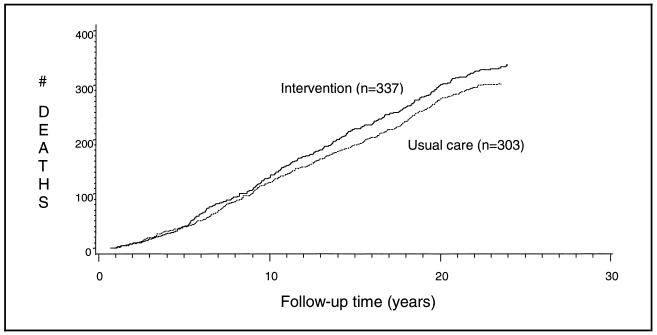


Fig. 1. Cumulative lung cancer deaths by study arm. Sample size was 4607 in the intervention arm **(solid line)** and 4585 in the usual-care arm **(dashed line). Numbers in parentheses** are the numbers of lung cancer deaths as of December 31, 1996. The National Death Index was used, as described in the text, to follow-up Mayo Lung Project participants for whom vital status on December 31, 1996, was unknown.

Table 2. Mortality in the Mayo Lung Project, as of December 31, 1996

Cause of death*	Deaths, No. (%)		Mortality rate (95% confidence interval) per 1000 person-years	
	Intervention arm (n = 4607)	Usual-care arm (n = 4585)	Intervention arm (76 760.7 person-years)	Usual-care arm (76 772.4 person-years)
Lung cancer	337 (7)	303 (7)	4.4 (3.9–4.9)	3.9 (3.5–4.4)
Causes other than lung cancer	2148 (47)	2133 (47)	28.0 (26.8–29.2)	27.8 (26.6–29.0)
Cancers other than lung cancer	403 (9)	391 (9)	5.3 (4.8–5.8)	5.1 (4.6–5.6)
Chronic obstructive pulmonary disease	156 (3)	149 (3)	2.0 (1.7–2.4)	1.9 (1.6–2.3)
Ischemic heart disease	816 (18)	816 (18)	10.6 (9.9–11.4)	10.6 (9.9–11.4)
Other respiratory causes	60 (1)	44 (1)	0.8 (0.6–1.0)	0.6 (0.4–0.8)
Other	712 (15)	733 (16)	9.3 (8.6–10.0)	9.5 (8.9–10.3)
All causes	2493 (54)	2445 (53)	32.5 (31.2–33.8)	31.8 (30.6–33.1)

*Seventeen participants (eight in the intervention arm and nine in the usual-care arm) had unknown causes of death.

LOW-DOSE CT SCREENING

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2006 VOL. 355 NO. 17

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

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*The International Early Lung Cancer Action Program investigators are listed in the Appendix.

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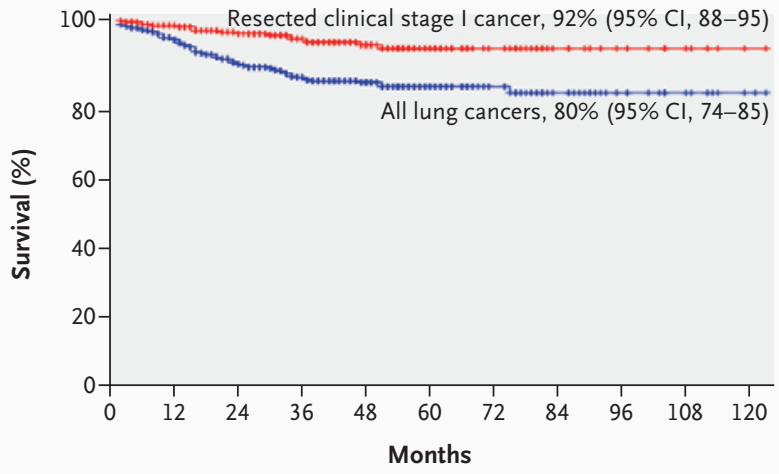

No. at Risk											
All participants	484	433	356	280	183	90	50	28	16	9	2
Participants undergoing resection	302	280	242	191	120	59	34	18	12	7	1

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

The National Lung Screening Trial:

Overview and Study Design [Gatsonis et al. Radiology: Volume 258: Number 1, January 2011]

The National Lung Screening Trial (NLST) is a randomized multicenter study comparing low-dose helical computed tomography (CT) with chest radiography in the screening of older current and former heavy smokers for early detection of lung cancer, which is the leading cause of cancer-related death in the United States. Five-year survival rates approach 70% with surgical resection of stage IA disease; however, more than 75% of individuals have incurable locally advanced or metastatic disease, the latter having a 5-year survival of less than 5%. It is plausible that treatment should be more effective and the likelihood of death decreased if asymptomatic lung cancer is detected through screening early enough in its preclinical phase. **For these reasons, there is intense interest and intuitive appeal in lung cancer screening with low-dose CT**. The use of survival as the determinant of screening effectiveness is, however, confounded by the well-described biases of lead time, length, and overdiagnosis. Despite previous attempts, no test has been shown to reduce lung cancer mortality, an endpoint that circumvents screening biases and provides a definitive measure of benefit when assessed in a randomized controlled trial that enables comparison of mortality rates between screened individuals and a control group that does not undergo the screening intervention of interest. The NLST is such a trial. The rationale for and design of the NLST are presented.

Sample Size Considerations

Preliminary computations of the required sample size for the NLST were made by using the approach of Taylor and Fontana, which is based on several simplifying assumptions and does not account for the number of screenings. The final computations were based on an elaboration of the approach of Hu and Zelen, modified to allow for staggered entry of participants and analyses based on calendar time instead of time on study. Parameters for the Hu-Zelen model are listed in Appendix E8 (online) and were estimated by using data from the Mayo Lung Project. **With 25 000 participants enrolled in each of years 1 and 2 of the trial, [i.e., 25,000 per arm, enrolled over 2 years]** statistical **power of 90% for detecting a 21% reduction in lung cancer mortality in the low-dose CT arm relative to the chest radiographic arm** may be achieved in an analysis conducted on events occurring through August 2008. Because of lags in data availability and entry, such an analysis would not occur until 2010. Therefore, we continued to collect information on lung cancer cases and deaths occurring through December 2009 so that information would not have to be obtained retroactively if needed.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

RESULTS

The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).

CONCLUSIONS

Screening with the use of low-dose CT reduces mortality from lung cancer. (Funded by the National Cancer Institute; National Lung Screening Trial ClinicalTrials.gov number, NCT00047385.)

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD 20892-7346, or at bergc@mail.nih.gov.

*A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

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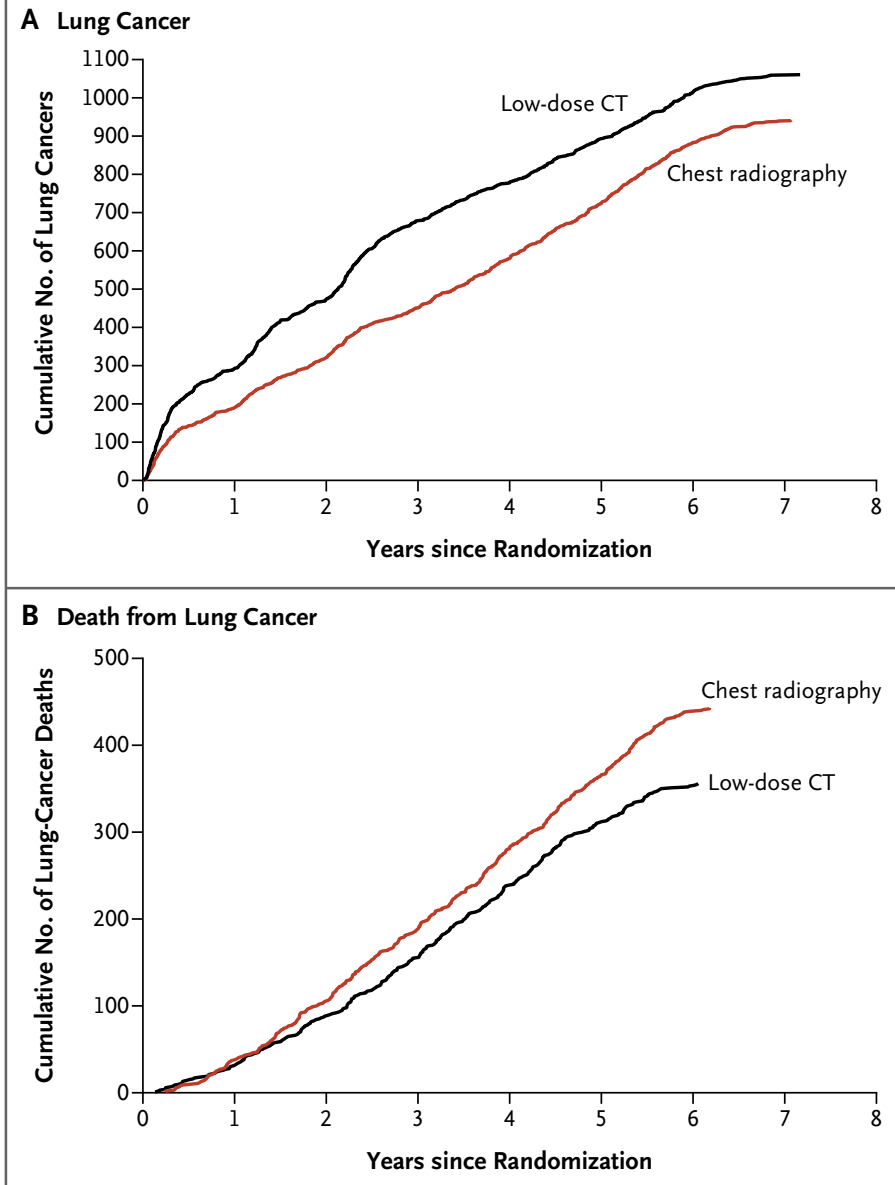

Figure 1. Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.

The number of lung cancers (Panel A) includes lung cancers that were diagnosed from the date of randomization through December 31, 2009. The number of deaths from lung cancer (Panel B) includes deaths that occurred from the date of randomization through January 15, 2009.