1. Refer to the story "Is Scouting Safe?" – example 3/31 in the compendium handed out in class (and available under Resources in the class website).

i. Which is the *single biggest flaw* in the analysis of the scouting injuries [page 3]. List two others that might on their own might be major – but not nearly as large as the distortion produced by the *big one* !
This is the question I asked last year, and most students didn't recognize the flawed person-time calculations. If you don't either, come back and answer i. once you have read ii. and answered iii.

ii. {*for input to iii, i.e. not a question per se*} Since it is not clear how the Statistics Canada data that went into the calculations were collected, it is not clear how the 1.1% was arrived at. Therefore, although it probably wasn't arrived at this way, I have *assumed, for the sake of this exercise* that the 1.1% was a *1-year cumulative incidence* from which I can then back-calculate to the daily (or hourly) incidence density.[1]

I assumed that the scouting authorities had used the classic and fundamental epidemiologic formula [*cf. Rothman 1986, Ch 3, pp29-32, available under Resources*]

$$CI_{jan1-dec31} = 1 - \exp\left[-\int_0^{365} ID(t)\delta t\right] = 0.011,$$

where ID(t), the incidence density function [for the event of (1st) hospitalization during 1990] is *assumed (for this exercise)* constant over the yea.

I was able, from this equation, to calculate the value of $ID(t)$, and express it as the average number of hospitalizations per child-day or per child-hour [making the simplifying assumption that children are at the same risk of hospitalization for each of the 24 hours of every day].

I did so (and you could too) by re-arranging the equation and taking the (natural) log. I back-calculated that (to 6 dp) the integral, ie., the area under the ID function (ie under the $ID(t)$ function plotted as a function of time) over the full year is 0.011061. Since the function was assumed constant over the 1 year, this means that the ID was 0.011061 events per child-year, or $0.011061/(365 \times 24)$ events per child-hour, i.e., 1.26 events per 10^6 child-hours. [This is *very* close to what I would have obtained if I treated the 1.1 not as a proportion or percentage, but as an incidence density of 1.1 events per 100 child-years.]

iii. If Scouting members spend 2 hours per week in activities during the course of a normal 30-week Scouting year, and 2 weeks (24/7) in summer camps, how many Scouting-activity hours (SA-hrs) are contributed by 1000 scouts over the course of 1 year (including the 2 full weeks in the summer)? From this, calculate an incidence density *ratio*, i.e.,

$$\frac{\text{1 hospitalization } \div \text{ SA-hrs}}{\text{incidence density obtained in (ii)}}$$

{you can also call it an (incidence) *rate ratio*}.

Comment on the difference between this and the rate ratio implied by the magazine article – and (if necessary) revise your answer to i.

2. Refer to example 7 "Extended work duration and the risk of self-reported percutaneous injuries in interns". From Table 1 (the full article is available, if interested, in the resources) the reported percutaneous Injury (PI) rate for obstetrics/gynecology (OB/GYN) residents was 0.0975 injuries/Intern-Month (I-M).

i. Using this incidence rate, calculate the probability that an average-risk ob/gyn resident would have no (or the complement, at least one), percutaneous Injury by the end of (a) 1 month (b) 12 months of experience? i.e. what is the probability of 'surviving' these amounts of experience without a PI? The complement is often referred to as 'cumulative incidence' or 'risk'. *Hint*: either use the (more general) formula for the relationship between incidence density (or event rate) and cumulative incidence i.e. the 'fundamental equation' used in question 1,[2] or in this case (since the rate is assumed to be constant over time), by treating the number of events in the (say 12 month) interval in question as a Poisson random variable with expectation $\mu = 12 \times 0.0975$, and calculating the probability of 0 events in that time interval.

[1] One possibility is that they simply divided the number of (first-for-the-child-that-year) hospitalizations in 1990 for persons in the aged 5-19 age-group by (365 × the estimated mid-1990 population of persons in that age-group). If this were the case, they should have expressed the ID as 1.1 cases per 100-child-years, not as a proportion (0.011) or as a percentage (1.1%). Epidemiology is applied common sense, but the subtleties are often overlooked by well-meaning amateurs.

[2] *See Ch 3 of Rothman 1986, or see the note "from incidence density to cumulative incidence, and back " handed out in class; Rothman 2002 covers this "constant ID" case in pp33-38 of Chapter 3 – cf Resources*

ii. What would the 6- and 12-month 'injury-free-survival' be if the incidence density varied linearly from: (a) 0.070/I-M at $t = 0$ to 0.130/I-M at $t = 12$ (b) 0.130/I-M to 0.070/I-M (c) 0.007/I-M to 0.013/I-M?

Hint: First plot the ID function. In this case, since the ID functions are linear, their integrals are just the areas of trapezoids, so you don't have to rely on calculus to calculate them.

Also, you can think of the integral of ID(t) over the time span in question as the *expected* number of events if there was always 1 (not necessarily the same) individual at risk for the full time span involved in the integral. It is easier to think of the continuous time at risk in the context of a work station where whenever the machine fails, it is immediately replaced by another one – see the notes on 'from incidence density to cumulative incidence, and back.'

iii. What approximation suggests itself for case (c) in (ii)? Can you develop a rule-of-thumb?

3. The following questions (relating to discrete-in-time acts, similar to repeated 'Russian roulette') are based on part of a letter to Editor of The Lancet, May 21, 1994:

> Mastro estimated the probability of HIV-1 transmission, per sexual contact, from female prostitutes to male military prostitutes in Northern Thailand. His conservative estimate of the transmission probability, based on all men, was 0.031 (95% CI 0.025 - 0.040). In a subgroup of men not reporting a history of other sexually transmitted diseases (STDs) his estimate was 0.012 (0.006 - 0.025). He attributes this unexpectedly high value to the possible presence of STDs in female prostitutes (which may have enhanced HIV transmission) and/or high levels of infectivity among the prostitutes who are likely to be at an early stage of HIV infection.
>
> Mastro apparently overlooks these explanations and assumes that the probability of transmission of HIV between regular partners would be the same as that in prostitute-client contacts. He then used this probability of 0.031 to calculate that over 90% of initially uninfected regular partners of seropositive persons would acquire infection over 1 year. This is inconsistent with data from prospective studies in developing countries suggesting seroconversion rates among HIV-discordant partners of about 10% per year. If it is assumed that couples on average have two sexual contacts per week, then on the basis of simple probability calculations, this gives an average transmission probability per sexual contact of about 0.001 (over 30 times smaller than the conservative estimate of Mastro)

i. Use the Binomial distribution with $\pi = 0.031$ to arrive at an estimate of "over 90%" [second sentence of paragraph 2]; assume two sexual contacts per week. *Hint*: instead of calculating the probability of at least one transmission, it is easier to first calculate its complement, the probability of no transmissions.

ii. Assuming again two contacts per week, do the *reverse* calculation [*from* the 10% 1-year seroconversion risk] that produces an estimate of "about 0.001" [last sentence of paragraph 2].

iii. The 'per-act' transmission probability for H*P*V is thought to be much higher than it is for H*I*V [cf Pubmed for work of Ann Burchell - one of our senior PhD students]. Assuming a frequency of sexual intercourse of 2 /week with an infected partner, what would the 3-month cumulative incidence (seroconversion risk) be if (a) the per-act transmission probability was 10%? (b) this per-act transmission probability could be halved by condom use?

You might be interested to adapt the "Russian Roulette" `R` *code under Resources to see how cumulative incidence is determined by the per-act probabilities and the number of acts.*

4. Refer to the "Women are Safer Pilots" story (example 4/31).

Suppose we are interested in the rate of accidents in women relative to men.

i. Explain why we cannot estimate the incidence density *difference*, but we can (with some assumptions) estimate the incidence density *ratio*.

ii. Assume that on average, the women pilots fly just as many hours as the men pilots, and that all other relevant factors are equal [although they probably are not!]. Calculate a point estimate of the IDR, and find, in Rothman 2002 (ch 7) or elsewhere, the most appropriate formula to calculate a CI for the IDR from the data provided.

iii. Repeat (ii), but now assume that on average the women pilots fly half as many hours as the men.

iv. Does the *structure* of this example have any similarities with that of example 10/31, where, presumably, the (implied) epidemiologic question behind the reference to 'virtue' is 'do Essex girls have more g.u. tract infections (or are more likely to attend g.u. medicine clinics?) than non-Essex girls? Imagine that we we combine the data for all with those with the name Tracey, Sandra or Sharon, and compare their visit rate with that of similar-aged women who have other names. What is our (point) estimate of the I.D.R.?

5. Refer to the "Estimability" example (example 31/31).

i. Reproduce Miettinen's calculations of the 30-year risk of bladder cancer for smokers and for non-smokers (this is a *projected* or *theoretical* risk, assuming the incidence densities that applied in 1970 still apply – this is the same assumption we make when we calculate life expectancy from age-specific death rates observed in a narrow calendar-time window.) Note: his calculations use that same fundamental relation between incidence density and cumulative incidence(risk) that we have used above.

ii. Why does the approximation he referred to give such good answers in this case? How well (or badly) would the approximation work as if we were interested in the cumulative risk of *death from any cause* over the same 30-year age span from 50-80, where the incidence densities for Quebec males, based on 2000-2002 data, are approximately[3]

Age band:	50-55	55-60	60-65	65-70	70-75	75-80
Deaths/10^5PY:	450	750	1250	2100	3500	5500

iii. In order, in each age band, to subdivide the overall age-specific incidence density into separate incidence densities for those with and without a history of smoking, Miettinen relies on the *population attributable fractions* or as he called them, *etiologic* fractions (EFs). For example, in the first age band the overall incidence density is $30/10^5$PY. The calculated EF is 0.74 (PAR: 74%). This means that 26% of the overall incidence density is "background'. Thus, even if there were no smokers, i.e. *if all were non-smokers*, the overall incidence density would have been 26% of $30/10^5$PY, i.e., $8/10^5$PY. The corresponding I.D. for the *smokers* is calculated so that the two have a weighed average of 10^5PY.

• Calculate the EF value of 74% by the (Levin, 1953) formula you learned in EPIB601.

• Calculate the EF value of 74% by the (Miettinen 1974) formula used in example 31.

For more on the Miettinen 1974 formula, refer to the article "A heuristic approach to the formulas for population attributable fraction" handed out in class.

[3] Life Tables, Canada, Provinces and Territories '95-'97 and 2000-2002 [Statistics Canada] see `http://www.medicine.mcgill.ca/epidemiology/hanley/bios601/Epidemiology2/`

Historical and Literary Corner – may also help in visualizing incidence density!

The Vision of Mirza & Incidence Density [if in a hurry, skip to • on p.4]

Joseph Addison [1672-1719]

> Omnem, qu nunc obducta tuenti
> Mortales hebetat visus tibi, et humida circum
> Caligat, nubem eripiam. 1
> Virgil, AEneid, ii. 604.

WHEN I was at Grand Cairo, I picked up several oriental manuscripts, which I have still by me. Among others I met with one entitled The Visions of Mirza, which I have read over with great pleasure. I intend to give it to the public when I have no other entertainment for them, and shall begin with the first vision, which I have translated word for word, as follows:

On the fifth day of the moon, which according to the custom of my forefathers I always keep holy, after having washed myself and offered up my morning devotions, I ascended the high hills of Baghdad, in order to pass the rest of the day in meditation and prayer. As I was here airing myself on the tops of the mountains, I fell into a profound contemplation on the vanity of human life, and passing from one thought to another, Surely, said I, man is but a shadow, and life a dream. Whilst I was thus musing, I cast my eyes towards the summit of a rock that was not far from me, where I discovered one in the habit of a shepherd, with a little musical instrument in his hand. As I looked upon him he applied it to his lips, and began to play upon it. The sound of it was exceeding sweet, and wrought into a variety of tunes that were inexpressibly melodious and altogether different from anything I had ever heard. They put me in mind of those heavenly airs that are played to the departed souls of good men upon their first arrival in Paradise, to wear out the impressions of the last agonies, and qualify them for the pleasures of that happy place. My heart melted away in secret raptures.

I had often been told that the rock before me was the haunt of a genius; and that several had been entertained with music who had passed by it, but never heard that the musician had before made himself visible. When he had raised my thoughts by those transporting airs which he played, to taste the pleasures of his conversation, as I looked upon him like one astonished, he beckoned to me, and by the waving of his hand directed me to approach the place where he sat. I drew near with that reverence which is due to a superior nature; and as my heart was entirely subdued by the captivating strains I had heard, I fell down at his feet and wept. The genius smiled upon me with a look of compassion and affability that familiarized him to my imagination, and at

once dispelled all the fears and apprehensions with which I approached him. He lifted me from the ground, and taking me by the hand, Mirza, said he, I have heard thee in thy soliloquies; follow me.

He then led me to the highest pinnacle of the rock, and placing me on the top of it, Cast thy eyes eastward, said he and tell me what thou seest. • I see, said I, a huge valley and a prodigious tide of water rolling through it. The valley that thou seest, said he, is the Vale of Misery, and the tide of water that thou seest is part of the great tide of eternity. What is the reason, said I, that the tide I see rises out of a thick mist at one end, and again loses itself in a thick mist at the other? What thou seest, said he, is that portion of eternity which is called time, measured out by the sun, and reaching from the beginning of the world to its consummation. Examine now, said he, this sea that is thus bounded by darkness at both ends, and tell me what thou discoverest in it. I see a bridge, said I, standing in the midst of the tide. The bridge thou seest, said he, is human life; consider it attentively. Upon a more leisurely survey of it I found that it consisted of more than threescore and ten entire arches, with several broken arches, which, added to those that were entire, made up the number to about a hundred. As I was counting the arches, the genius told me that this bridge consisted at first of a thousand arches; but that a great flood swept away the rest, and left the bridge in the ruinous condition I now beheld it. But tell me further, said he, what thou discoverest on it. I see multitudes of people passing over it, said I, and a black cloud hanging on each end of it. As I looked more attentively, I saw several of the passengers dropping through the bridge into the great tide that flowed underneath it; and upon further examination, perceived there were innumerable trap-doors that lay concealed in the bridge, which the passengers no sooner trod upon, but they fell through them into the tide and immediately disappeared. These hidden pitfalls were set very thick at the entrance of the bridge, so that throngs of people no sooner broke through the cloud, but many of them fell into them. They grew thinner towards the middle, but multiplied and lay closer together towards the end of the arches that were entire.

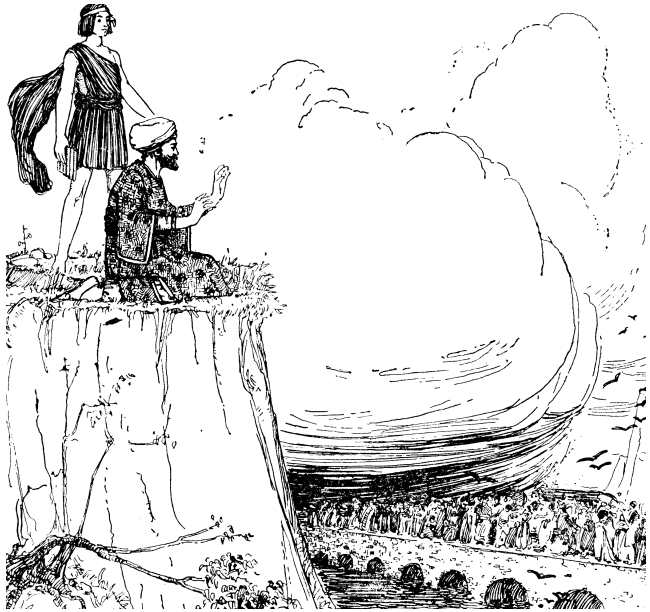
There were indeed some persons, but their number was very small, that continued a kind of hobbling march on the broken arches, but fell through one after another, being quite tired and spent with so long a walk.

I passed some time in the contemplation of this wonderful structure, and the great variety of objects which it presented. My heart was filled with a deep melancholy to see several dropping unexpectedly in the midst of mirth and jollity, and catching at everything that stood by them to save themselves. Some were looking up towards the heavens in a thoughtful posture, and in the midst of a speculation stumbled and fell out of sight. Multitudes were very busy in the pursuit of bubbles that glittered in their eyes and danced before them, but often when they thought themselves within the reach of them their footing failed and down they sunk. In this confusion of objects, I observed some with scimitars in their hands, and others with urinals, who ran to and fro upon the bridge, thrusting several persons on trap-doors which did not seem to lie in their way, and which they might have escaped had they not been thus forced upon them.

The genius, seeing me indulge myself on this melancholy prospect, told me I had dwelt long enough upon it, Take thine eyes off the bridge, said he, and tell me if thou seest anything thou dost not comprehend. Upon looking up, What mean, said I, those great flights of birds that are perpetually hovering about the bridge, and settling up it from time to time? I see vultures, harpies, ravens, cormorants, and among many other feathered creatures several little winged boys that perch in great numbers upon the middle arches, These, said the genius, are Envy, Avarice, Superstition, Despair, Love, with the like cares and passions that infest human life.

I here fetched a deep sigh. Alas, said I, man was made in vain: how is he given away to misery and mortality, tortured in life, and swallowed up in death! The genius being moved with compassion towards me, bid me quit so uncomfortable a prospect. Look no more, said he, on man in the first stage of his existence, in his setting out for eternity; but cast thine eye on that thick mist into which the tide bears the several generations of mortals that fall into it. I directed my sight as I was ordered, and (whether or no the good genius strengthened it with any supernatural force, or dissipated part of the mist that was before too thick for eye to penetrate) I saw the valley opening at the farther end, and spreading forth into an immense ocean that had a huge rock of adamant running through the midst of it, and dividing it into two equal parts. The clouds still rested on one half of it, insomuch that I could discover nothing in it; but the other appeared to me a vast ocean planted with innumerable islands, that were covered with fruits and flowers, and interwoven with a thousand little shining seas that ran among them. I could see persons dressed in glorious habits with garlands upon their heads, passing among the trees, lying down by the sides of fountains, or resting on beds of flowers; and could hear a confused harmony of singing birds, falling waters, human voices, and musical instruments. Gladness grew in me upon the discovery of so delightful a scene. I wished for the wings of an eagle that I might fly away to those happy seats; but the genius told me there was no passage to them except through the gates of death that I saw opening every moment upon the bridge. The islands, said he, that lie so fresh and green before thee, and with which the whole face of the ocean appears spotted as far as thou canst see, are more in number than the sands on the seashore; there are myriads of islands behind those which thou here discoverest, reaching

farther than thine eye, or even thine imagination can extend itself. These are the mansions of good men after death, who, according to the degree and kinds of virtue in which they excelled, are distributed amount these several islands, which abound with pleasures of different kinds and degrees suitable to the relishes and perfections of those who are settled in them; every island is a paradise accommodated to its respective inhabitants. Are not these, O Mirza, habitations worth contending for? Does life appear miserable that gives thee opportunities of earning such a reward? Is death to be feared that will convey thee to so happy an existence? Think not man was made in vain who has such an eternity reserved for him. I gazed with inexpressible pleasure on these happy islands. At length, said I, Show me now, I beseech thee, the secrets that lie hid under those dark clouds which cover the ocean on the other side of the rock of adamant. The genius making me no answer, I turned me about to address myself to him a second time, but I found that he had left me; I then turned again to the vision which I had been so long contemplating; but, instead of the rolling tide, the arched bridge, and the happy islands, I saw nothing but the long valley of Baghdad, with oxen, sheep, and camels grazing upon the sides of it.



from `http://etc.usf.edu/clipart/17400/17410/mirza_17410.htm`

see also `http://www.dmvi.cardiff.ac.uk/imageDetail.asp?illus=LHF026`

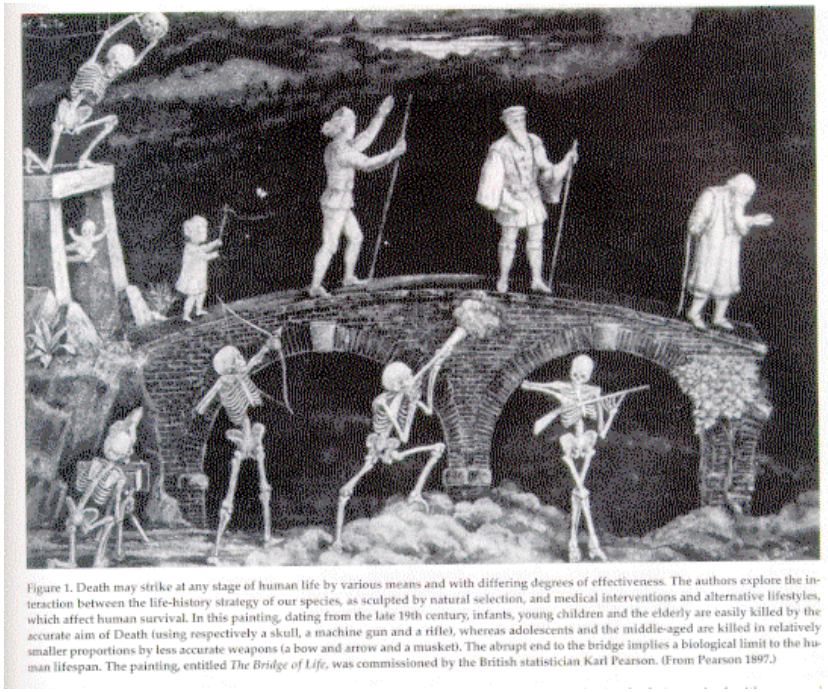


Figure 1. Death may strike at any stage of human life by various means and with differing degrees of effectiveness. The authors explore the interaction between the life-history strategy of our species, as sculpted by natural selection, and medical interventions and alternative lifestyles, which affect human survival. In this painting, dating from the late 19th century, infants, young children and the elderly are easily killed by the accurate aim of Death (using respectively a skull, a machine gun and a rifle), whereas adolescents and the middle-aged are killed in relatively smaller proportions by less accurate weapons (a bow and arrow and a musket). The abrupt end to the bridge implies a biological limit to the human lifespan. The painting, entitled *The Bridge of Life*, was commissioned by the British statistician Karl Pearson. (From Pearson 1897.)

The Bridge of Life. In Karl Pearson: The chances of death and other studies in evolution (1897).

Based on Addison's allegory ???