Causality and chance in recent pharmacovigilance signals of COVID-19 vaccines: what evidence for public health decisions?

Prof. Bernard Bégaud

Medical College – University of Bordeaux, France

Bordeaux Research Center on Population Health, Inserm U1219

Let’s start by killing the suspense

- Conception, development and marketing, within one year, of several anti COVID-19 vaccines will remain one of the biggest successes of modern pharma.
- Despite the unforgivable mistakes made (both methodological and communication), the benefit/risk balance remains excellent if the targets were chosen well.
- Beware not throwing out the baby with the bathwater.

Two questions, two concerns

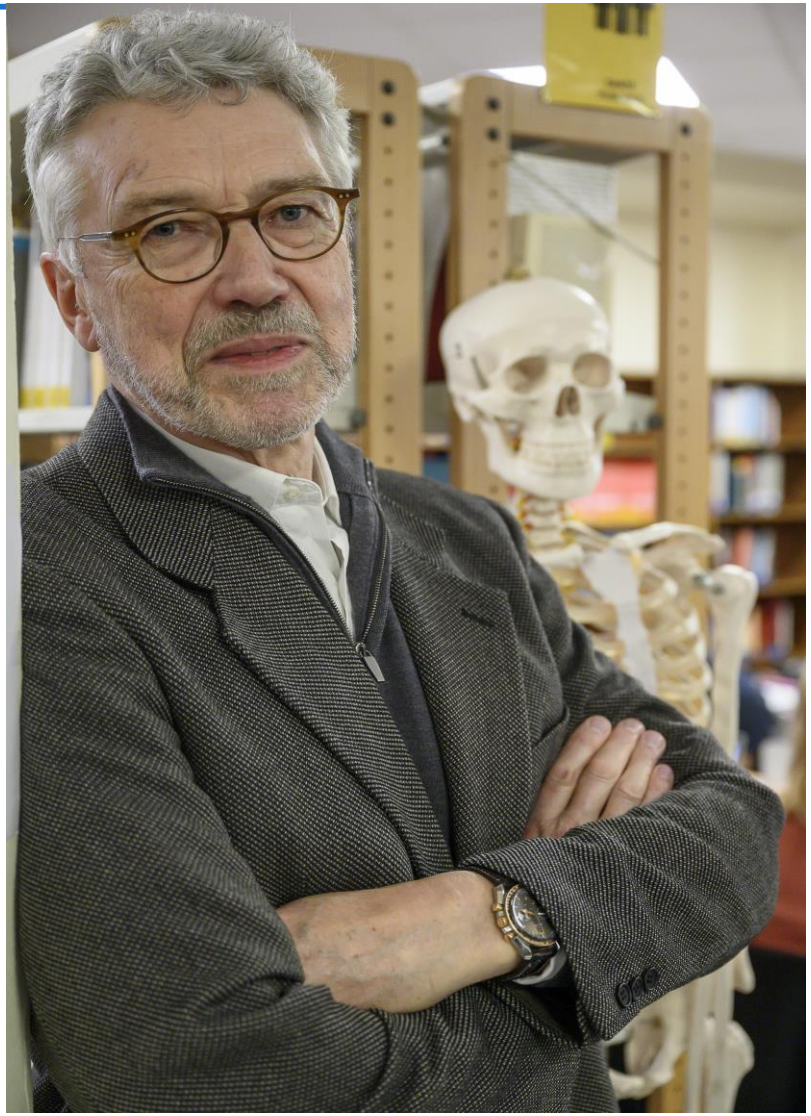
- The two questions to be addressed about the COVID-19 Astra Zeneca vaccine
  - *Is the occurrence of cases of venous thrombosis after vaccination coincidental or (at least in part) causal?*
  - *Based on this response, is the benefit/risk balance for this vaccine still excellent?*
- Vaccine hesitancy is fueled more by communication errors than by methodological errors leading to biased estimates.
- In the present case, we have had both.

Causal or coincidental?

- Answering the question is the purpose of causality assessment:
  - Self-evident causal relationship
  - Assessment at the individual level (case by case)
  - Assessment at the group level (the statistical oracle)

Self-evident causal relationship

- Example:
  - Before vaccination (left)
  - Two minutes after vaccination (right)



Causal or coincidental?

Answering this question is the purpose of causality assessment:

- At the individual level (1)
  - ✧ Expert judgment
    - Single expert
    - Group of experts
    - Delphi's process
  - ✧ Algorithms
  - ✧ Approaches based on probability distributions
    - Bayes' Theorem
    - Logistic model
- At the group level: the statistical oracle

(1) See: Bégaud B, Jones JK. *Assessing Causality from case-reports*. Chapter 14th In Brian Strom's *Textbok of Pharmacoepidemiology*. 3d ed.Wiley 2021.

Causal or coincidental?

Answering this question is the purpose of causality assessment:

- At the individual level
- At the group level: the statistical oracle
  - Experimental plans: clinical trials, pragmatic trials
  - Observational approaches
    - Classical pharmacoepidemiologic approaches: cohort, case-control, self-controlled designs
    - « Simplified » pharmacoepidemiologic approaches: case-population, observed *vs* expected

Observed *vs* expected

- On March 10th 2021, the EMA made reference to the observed *vs* expected approach:
- « *The number of thromboembolic events reported in vaccinated people seems not to be higher that seen in the general population* »
- Let’s illustrate the principle of such a comparison.

Observed versus expected

- On April 7th 2021: 62 cases of cerebral venous sinus thrombosis (CVST)
- 25 million vaccinated people
- Baseline incidence of CVST in the general population:
  - 5 per million per year (restrictive case definition)
  - 13.2 per million person-years (Coutinho. Stroke 2012)
  - 15.7/million/year (Devasagayan. Stroke 2016)

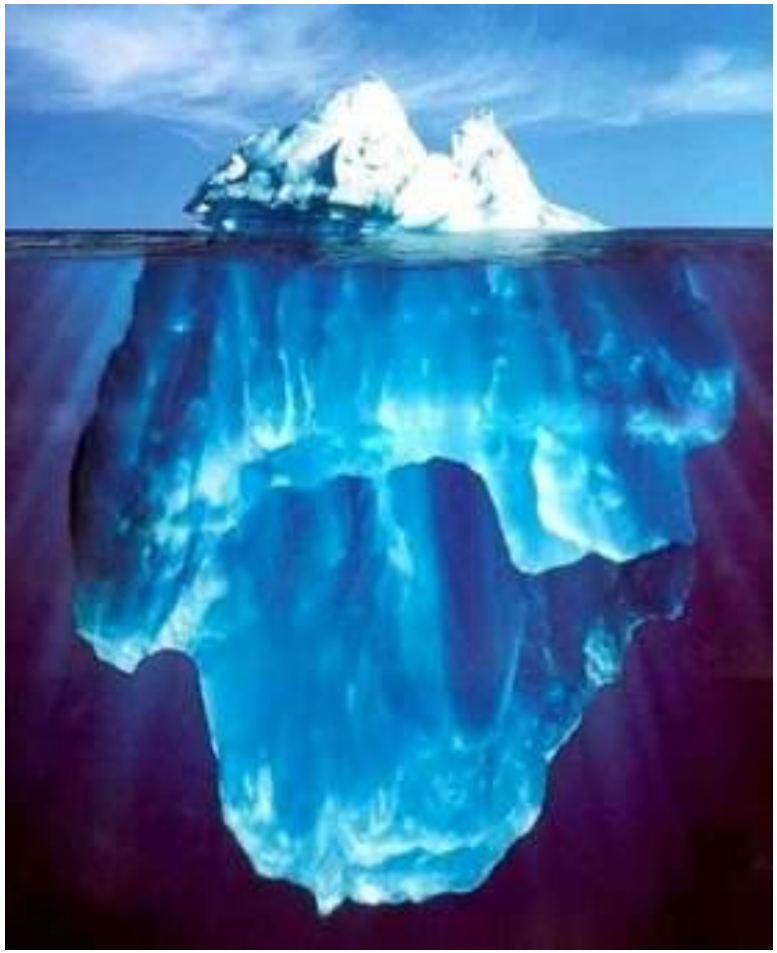
Observed versus expected (author's computations)

- Observed (reports received by EMA): 62 cases of CVST
- Expected under the null hypothesis of no association:
  - Low estimate: $(5/10^6)$ x 25,000,000 = 125 cases, or
  - High estimate: $(14/10^6)$ x 25,000,000 = 350 cases
- The observed number is 2 to 5.6 times lower than expected from chance in the vaccinated population!

Observed versus Expected (author's computations)

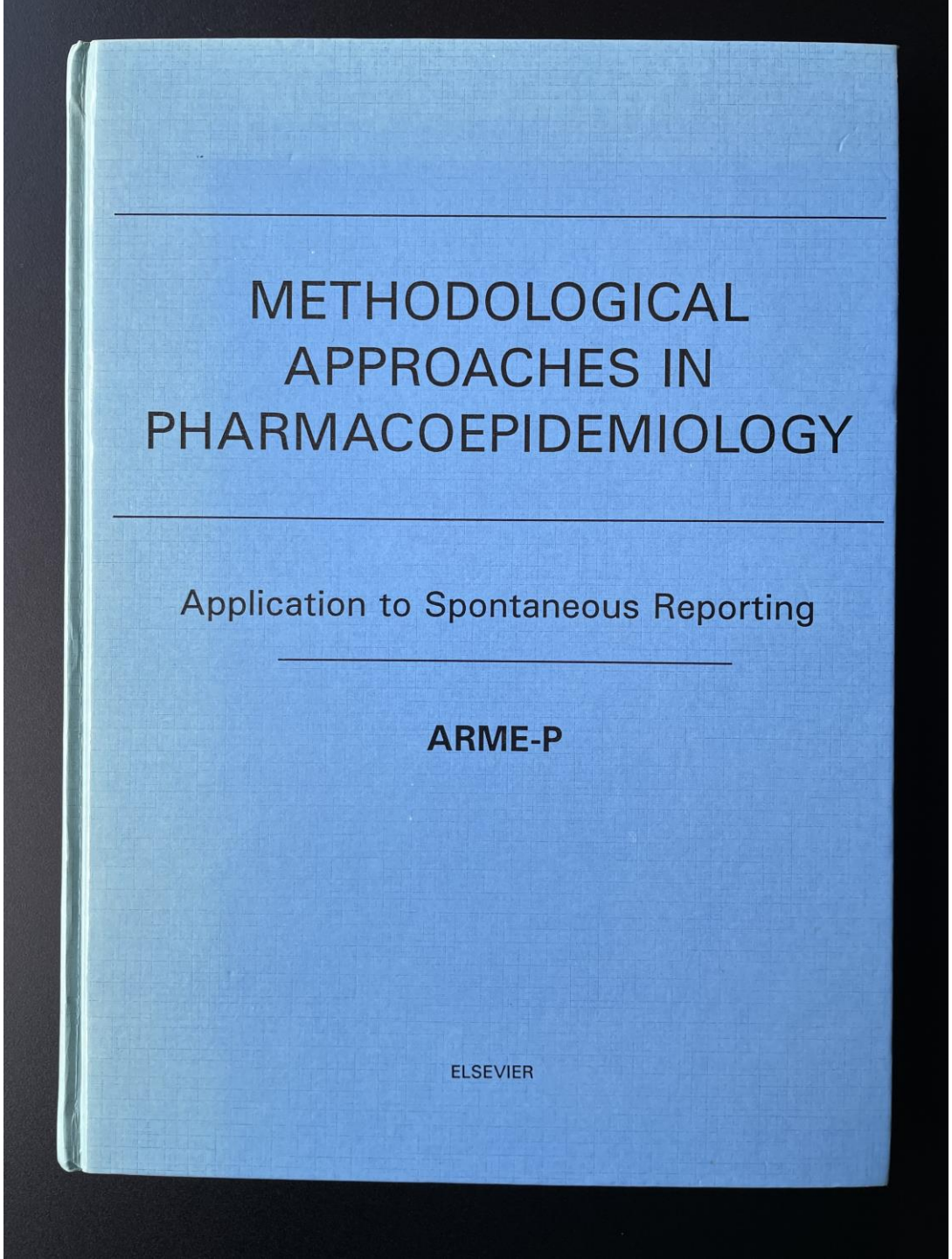
- At least three serious methodological errors have been made here:
  - 1. Forgetting the inescapable and always important under-reporting
  - 2. Using an inflated denominator
  - 3. Using inconsistent time-windows

#1. The inescapable under-reporting



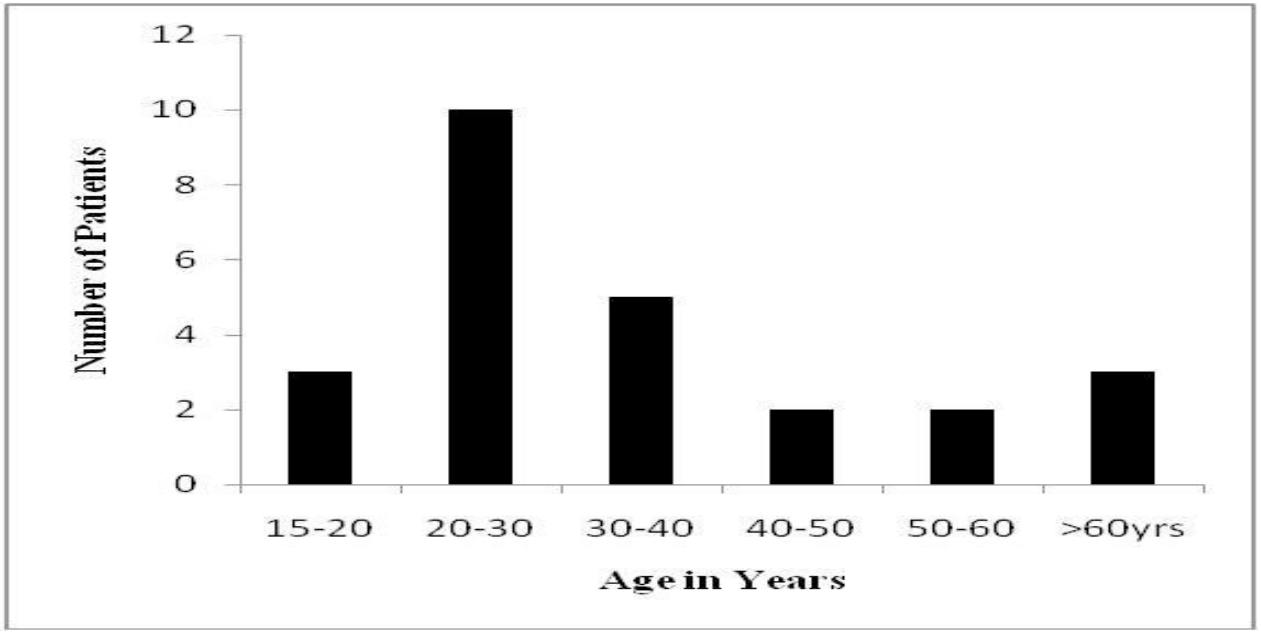
#1. The inescapable under-reporting

- Spontaneous reporting only catches a (small) proportion of relevant ADR cases, even when the event is severe or blipped up by media.
- Several studies (France, UK, USA) have shown that, on average, 5% of cases are actually reported to pharmacovigilance systems.
- Even if unknown, the actual number of CVST in persons vaccinated with Astra Zeneca was **certainly** higher than 62 (at least 5 to 10 times would be credible).


METHODOLOGICAL
APPROACHES IN
PHARMACOEPIDEMIOLOGY
Application to Spontaneous Reporting
ARME-P
ELSEVIER

#2. Using an inflated denominator

- When using a rate to quantify a risk, care must be taken that all the persons included in the denominator have *a priori* the same chance presenting the event studied. This was far from being the case here:



#3. Using inconsistent time-windows

- Observed/Expected comparison should be made on a predefined and relevant time-window.
- For example, if the 62 CVST cases were observed within the 2 weeks following injection, the question was: « *how many CVST cases were expected anyway (i.e. in the absence of vaccination) during this 2-week interval ?* »
- The computation should be obviously made for the **same time interval**; *i.e*. two weeks for both and not two weeks for one and one year for the other!

#3. Using inconsistent time-windows

- Probability of presenting by chance a CVST during a 2-week interval:
  - Low estimate: $(5/10^6) \times (2/52) = 0.19/10^6$
  - High estimate: $(14/10^6) \times (2/52) = 0.54/10^6$
- Expected number of coincidental CVSTs during the 2 weeks following the 25 million injections:
  - Low estimate: $(0.19/10^6) \times (25 \times 10^6)$ = **4.8 cases** and not 125
  - High estimate: $(0.54/10^6) \times (25 \times 10^6)$ = **13.5 cases** and not 350.

Wrapping up (author's personal computations and opinion)

- Number of CVST cases after AZ doses: >> 62
- 5 to 14 cases expected by chance (2-week time-window)
- O/E ratio: 4.3 to 24.8 (highly significant difference. Poisson)
- On this basis, it is clear that a signal does exist
- 😣
- It should be strengthened by:
  - Case by case assessment
  - Biological plausibility
  - More robust pharmacoepidemiologic approaches

The benefit/risk balance

- On March 10th 2021, the EMA stated to be « *firmly* ***convinced*** *that the benefits of the Astra Zeneca vaccine in preventing COVID-19, with its asociated risks of hospitalization and death, outweigh the risks of side effects* ».
- Were regulators and statistical modelling in agreement?

The benefit/risk balance

- The basic concept is simple:
  - The benefits (individual or populational) expected from the use of a medicine should always be much greater than the risk incurred.
- The statistical computation is fairly complex:
  - Therapeutic effect: a pharmacologic response expressed by almost all treated persons (65 to 97% for COVID vaccines)
  - Untoward effects:
    - Often not identified
    - Low to extremely low probability of occurrence
    - Occurring only if certain risk factors or traits are present.

OPUSCULES
MATHÉMATIQUES,
OU

MÉMOIRES sur différens sujets de GÉOMÉTRIE, de MÉCHANIQUE, D'OPTIQUE, D'ASTRONOMIE &c.

Par M. D'ALEMBERT, de l'Académie Françoiſe, des Académies Royales des Sciences de France, de Pruſſe & d'Angleterre, de l'Académie Royale des Belles-Lettres de Suéde, & de l'Inſtitut de Bologne.

TOME SECOND.

A PARIS,

Chez DAVID, rue & vis-à-vis la grille des Mathurins.

M. DCC. LXI.

AVEC APPROBATION ET PRIVILÉGE DU ROI.

ONZIÉME MÉMOIRE.

Sur l'application du Calcul des Probabilités à l'inoculation de la petite Vérole (a).

ON a tant écrit depuis quelques années pour & contre l'inoculation, & principalement en ſa faveur, que le Public doit être aujourd'hui plus que ſuffiſamment inſtruit ſur ce ſujet, & par conſéquent fatigué d'avance de tout ce qu'on pourroit ajouter encore, pour éclaircir ou pour embrouiller la queſtion. J'ai donc tout lieu de craindre que ce Mémoire n'ennuye déja par ſon ſeul titre ceux qui me font l'honneur de m'entendre. Je me propoſe au moins de ne pas les ennuyer long-tems; & pour leur tenir parole, j'entre promptement en matiere.

Cet écrit aura deux objets: 1°. de prouver que dans les calculs qu'on a faits juſqu'à préſent en faveur de l'inoculation, on n'a point encore, ce me ſemble, enviſagé la queſtion ſous ſon véritable point de vûe: 2°. que la

(a) Ce Mémoire a été lû à l'Aſſemblée publique de l'Académie Royale des Sciences, le 12 Novembre 1760.

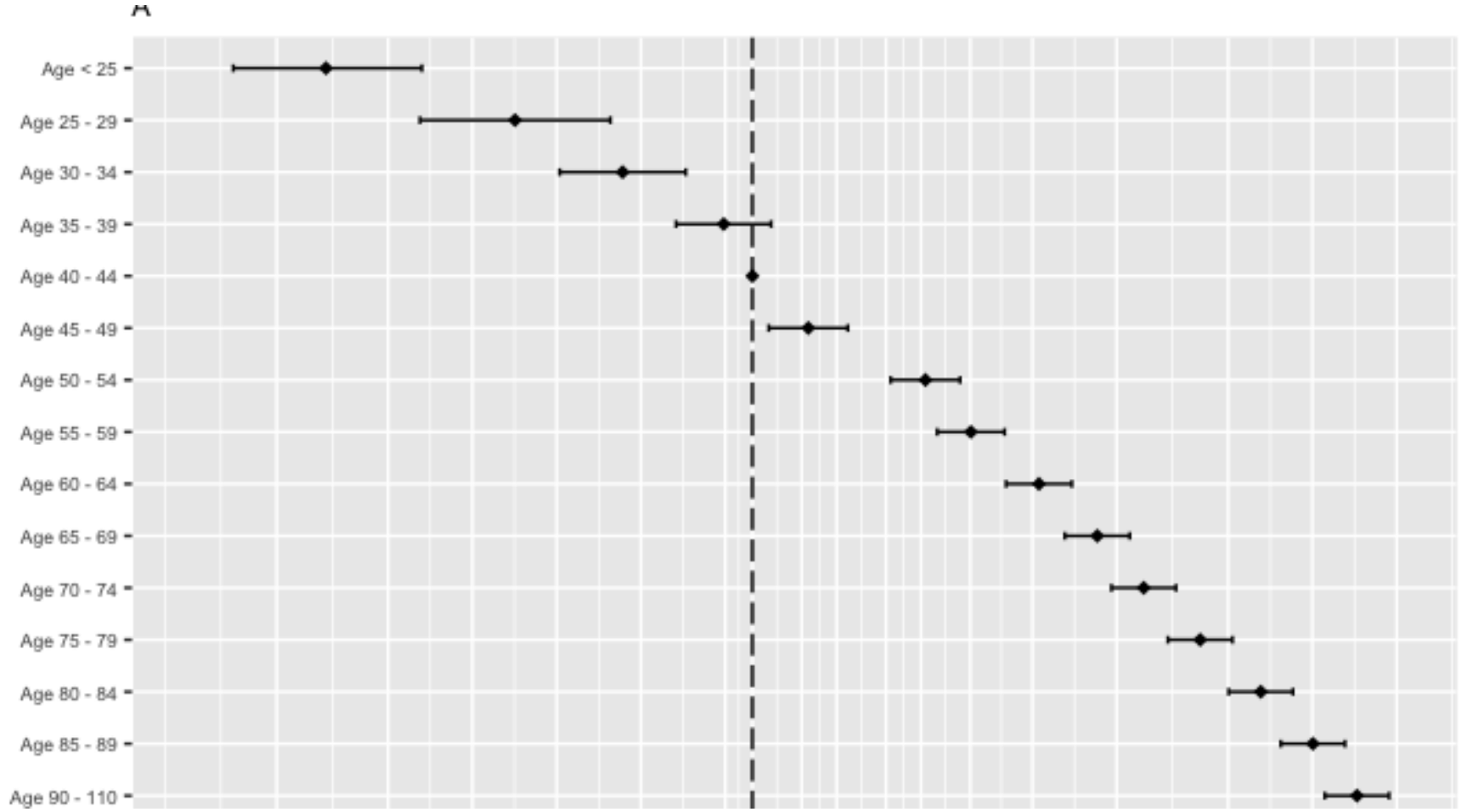
lomne marquera pour chaque âge le rapport de m à n, & une huitiéme celui de $n - m$ à n. La neuviéme colomne donnera le rapport de $K'k'$ à AK' (*fig.* 3.) pour chaque âge; c'eſt-à-dire, le rapport du nombre des morts de l'inoculation au nombre des inoculés. La dixiéme colomne ſera la valeur de $\int \frac{y\,dx}{k}$, c'eſt-à-dire, la vie moyenne propre à chaque âge, avant ou après la petite Vérole. La onziéme, la valeur de $\int \frac{z\,dx}{k} \times \frac{Ak'}{AK'}$, c'eſt-à-dire, la vie moyenne des inoculés. La treiziéme, le tems AR' que les inoculés peuvent eſpérer de vivre. La quatorziéme, la vie moyenne $\int \frac{u'\,dx}{k'} = \int \frac{y\,dx}{k} \times \frac{n}{n-m} - \int \frac{y\,dx\, e^{\int \frac{du}{y}}}{k(n-m)}{}^{m} = \int \frac{y\,dx}{k} \times \frac{n}{n-m} - \int \frac{m z\,dx}{k(n-m)}$, de ceux qui n'ont pas eu la petite Vérole; ou, ſi l'on veut, la quantité $\frac{m \int \omega\,dx}{k(n-m)}$, dont leur vie moyenne eſt plus courte que la vie moyenne générale $\int \frac{y\,dx}{k}$ de toutes les perſonnes du même âge, priſes indiſtinctement. La quinziéme enfin, le tems Af (*fig.* 4.) qu'ils peuvent raiſonnablement eſpérer de vivre, c'eſt-à-dire, celui où ils ſeront réduits à la moitié; on aura ainſi pour chaque âge le rapport de AR' (*fig.* 3.) à Af (*fig.* 4.).

18. Voilà tout ce que la théorie Mathématique peut

For modern vaccine pharmacoepidemiology: back to the 18th century!

- What we learned from d'Alembert (variolation against smallpox,1761):
  - Benefit/risk balance generally differs for the person and the population.
  - Vaccination imposes a risk of ADR for all while, for a given person, the gain is hypothetical (random): $P_{Bad} = P_{Inf} \times P_{Hosp\ or\ Death}$
  - The risk is « fixed » (one shot) but the gain is incremental, i.e. increases over time (assuming « life time » protection).
  - Estimating benefit/risk balance for the general population could be misleading and lead to inappropriate public health decisions:
    - Both risk and benefit generally vary greatly with age (often in opposite directions)
    - Consequently, the gain/risk balance depends on the age at which the vaccination is practiced (life expectancy plays a major role here).

How could we forget a risk modifier like this?



From the EPI-PHARE 2021 study

From 1761 to 2021

The two questions to be addressed about the COVID-19 Astra Zeneca vaccine:

- 1. Was the occurrence of cases of cerebral venous thrombosis after vaccination coincidental or, at least in part, causal?
- 2. If we retained « causal », does the benefit/risk balance of this vaccine remains good/excellent?

  And, for whom?

Proposed answers

- Question #1. 😯 Data available tend to support a causal role of the AZ vaccine (and other adenovirus vaccines?) in the occurrence of CVSTs.
- Question #2. ☐ Too many uncertainties remain to compete with d'Alembert (sad!). Among others:
  - Duration of vaccine protection: 8.5 months? Lifetime?
  - Duration of the COVID-19 Pandemic
  - The effectiveness of AZ vaccine against variants (present and future)
  - The availability of « safer » alternatives (vaccines or not) in the next future.

Comparing gain and risk

Age	Population	Covid deaths (14 months)	Death rate per 1000	One Covid death for	CVST risk
15 - 44	29,972,755	1000	0.033	29,973	High
45 – 64	17,416,533	7000	0.402	2488	Medium
65 - 74	7,647,494	15,000	1.96	510	Low
>74	6,892,491	78,000	11.32	88	Very low

Author’s computation for the whole pandemic period (January 2020 to April 2021) in France.

Modelling Benefit/Risk balance (1)

- Framework
  - France, actual statistics, assuming a fixed (not dynamic) population
- Vaccine
  - 100% population immunized within 3 months (actuarial method)
  - Protection: 80% (assumed constant accross ages)
- CVST
  - Baseline risk
    - 15 - 44 : 22 x 10^{-6}
    - 45 - 64 : 16 x 10^{-6}
    - 64 - 74 : 10 x 10^{-6}
    - > 74: 6 x 10^{-6}
  - Relative risk: 1.5 (assumed constant)
- Two scenari
  - B/R over one year, 2 doses (One-year protection)
  - B/R over 5 years, 2 doses (Protection > 5 years after complete vaccination)

Modelling Benefit/Risk balance (2)

	Scenario 1:	**2 doses, 1 year**	**Scenario 2:**	**2 doses, 5 years**
	Attr. CVSTs	*Covid deaths prevented*	*Attr.CVSTs*	*Covid deaths prevented*
15 - 44	660	601	660	3344
45 - 64	278	4167	278	23,367
65 - 74	76	8999	76	50,142
> 74	42	46,800	42	260,743

Modelling Benefit/Risk balance (3)

Results for one million vaccinated people:

	Attributable CVSTs	*Deaths prevented (one year)*	*Deaths prevented (five years)*
15 - 44	22	20	112
45 - 64	16	239	1342
65 - 74	10	1177	6557
> 74	6	6790	37,830

Wrapping up (1)

- Assuming that the Astra Zeneca vaccine is (and will remain) effective against variants, and without considering other associated ADRs, the benefit/risk balance remains *a priori* very good with a clear concern for young adults and, probably, particularly women (oral contraceptives?).
- Consequently, the risk of serious/fatal ADR should be < 1/30,000; << 1/30,000 if the vaccine protection lasted less than 14 months.
- In older adults (>64), the BR balance is clearly good.
- The same computation can/should be easily made for hospitalizations, long-lasting COVIDs, etc.

Wrapping up (2)

- The examples above concern the B/R balance at the individual level. It may be a priority to immunize young adults to stop the circulation and replication of COVID viruses in the population.
- From vaccines affairs, we learned that a good communication is more important than statistics: some fatal cases, *e.g.* in an healthy young women, can kill the product, even the campaign, more surely than a brillant computation.

Wrapping up (3)

- Statistics and modelling are a powerful tool for preparing and adjusting public health decisions.
- Results can be easily strengthened by sensitivity analyses.
- In the present case, it will be difficult to go further in the absence of information on the age and sex distributions of the reported CVST cases and on the distribution of the number of doses by age groups. 😟
- In any case, a specific pharmacoepidemiologic study should be carried out as soon as possible.

Thank you for your attention