

Epidemiológiai bevezetés

Solymosi Norbert

Kvantitatív állatorvosi epidemiológia

Járványtani és Mikrobiológiai Tanszék

Állatorvostudományi Egyetem



A 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system.

Findings

Seroprevalence was 5.0% (95% CI 4.7–5.4) by the point-of-care test and 4.6% (4.3–5.0) by immunoassay, with a **specificity–sensitivity** range of 3.7% (3.3–4.0; both tests positive) to 6.2% (5.8–6.6; either test positive), with no differences by sex and lower seroprevalence in children younger than 10 years (<3.1% by the point-of-care test). There was substantial **geographical variability**, with higher **prevalence** around Madrid (>10%) and lower in coastal areas (<3%). Seroprevalence among 195 participants with positive PCR more than 14 days before the study visit ranged from 87.6% (81.1–92.1; both tests positive) to 91.8% (86.3–95.3; either test positive). In 7273 individuals with anosmia or at least three symptoms, seroprevalence ranged from 15.3% (13.8–16.8) to 19.3% (17.7–21.0). Around a third of seropositive participants were asymptomatic, ranging from 21.9% (19.1–24.9) to 35.8% (33.1–38.5). Only 19.5% (16.3–23.2) of symptomatic participants who were seropositive by both the point-of-care test and immunoassay reported a previous PCR test.

Results

Of the 8910 patients with Covid-19 for whom discharge status was available at the time of the analysis, a total of 515 died in the hospital (5.8%) and 8395 survived to discharge. The factors we found to be independently associated with an increased risk of in-hospital death were an age greater than 65 years (mortality of 10.0%, vs. 4.9% among those \leq 65 years of age; **odds ratio**, 1.93; 95% **confidence interval [CI]**, 1.60 to 2.41), coronary artery disease (10.2%, vs. 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, vs. 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, vs. 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, vs. 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40), and current smoking (9.4%, vs. 5.6% among former smokers or nonsmokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47). No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; odds ratio, 1.23; 95% CI, 0.87 to 1.74).



Covid-19 antibody testing

Diagnostic accuracy of three serological tests

Summary

Current evidence does not support the continued use of existing point-of-care covid-19 serology tests with the LFIA method.
Only two studies evaluated performance at the point of care

Study design

Systematic review and meta-analysis

Sensitivity estimated from people with confirmed covid-19

Specificity estimated mostly using pre-epidemic samples, or low risk individuals

Data sources

40 studies

29 842 tests

More than one sample may have originated from the same participant

Comparison**ELISA**

Enzyme Linked Immunosorbent Assays

LFIA

Lateral Flow Immunoassays

CLIA

Chemiluminescent Immunoassays

Results

Under 10% prevalence

TRUE result**FALSE result**

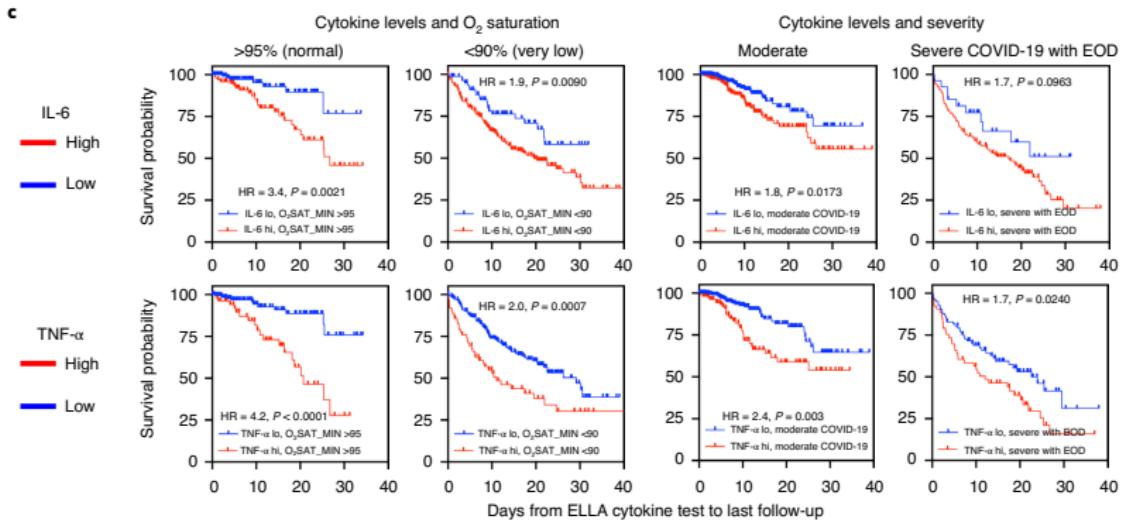


Fig. 4 | Cytokine levels correlate with severity and independently predict survival. Correlation of cytokine levels with established inflammatory and severity measurements. **a**, Correlation of each cytokine with each metric ($n=1,106$ for fever, $n=1,112$ for O_2 saturation, $n=1,023$ for CRP, $n=926$ for D-dimer, $n=1,017$ for ferritin, $n=1,038$ for platelets and $n=1,023$ for disease severity score), using the same univariate and multivariate analyses as in the Fig. 2 legend. Error bar indicates the median \pm 95% CI. **b**, Competing risk analysis ($n=671$) showing survival differences by IL-6 and TNF- α levels, after adjusting the following variables: IL-6, IL-8, TNF- α , IL-1 β , age, sex, race/ethnicity, smoking status, asthma, atrial fibrillation, cancer, CHF, CKD, COPD, diabetes, hypertension, sleep apnea, severity, systolic blood pressure max, O_2 saturation min, D-dimer, albumin, calcium, chloride and platelet count. **c**, Kaplan-Meier univariate analyses of survival by IL-6 and TNF- α levels in patients with normal ($n=257$), low ($n=258$) or very low ($n=287$) O_2 saturation, or in patients with moderate ($n=588$) versus severe COVID-19 with end organ damage ($n=136$), as measured at the first available test.

EDITORIAL

Will COVID-19 be evidence-based medicine's nemesis?

Trisha Greenhalgh *

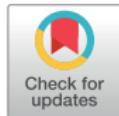
Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

* trish.greenhalgh@phc.ox.ac.uk

Once defined in rhetorical but ultimately meaningless terms as “the conscientious, judicious and explicit use of current best evidence in making decisions about the care of individual patients” [1], evidence-based medicine rests on certain philosophical assumptions: a singular truth, ascertainable through empirical enquiry; a linear logic of causality in which interventions have particular effect sizes; rigour defined primarily in methodological terms (especially, a hierarchy of preferred study designs and tools for detecting bias); and a deconstructive approach to problem-solving (the evidence base is built by answering focused questions, typically framed as ‘PICO’—population-intervention-comparison-outcome) [2].

The trouble with pandemics is that these assumptions rarely hold. A pandemic-sized problem can be framed and contested in multiple ways. Some research questions around COVID-19, most notably relating to drugs and vaccines, are amenable to randomised controlled trials (and where such trials were possible, they were established with impressive speed and efficiency [3, 4]). But many knowledge gaps are broader and cannot be reduced to PICO-style questions. Were care home deaths avoidable [5]? Why did the global supply chain for personal protective equipment break down [6]? What role does health system resilience play in controlling the pandemic [7]? And so on.

Against these—and other—wider questions, the neat simplicity of a controlled, interven-



Check for
updates

 OPEN ACCESS

Greenhalgh (2020)

QEpi (2022.II.7.)

Bevezetés

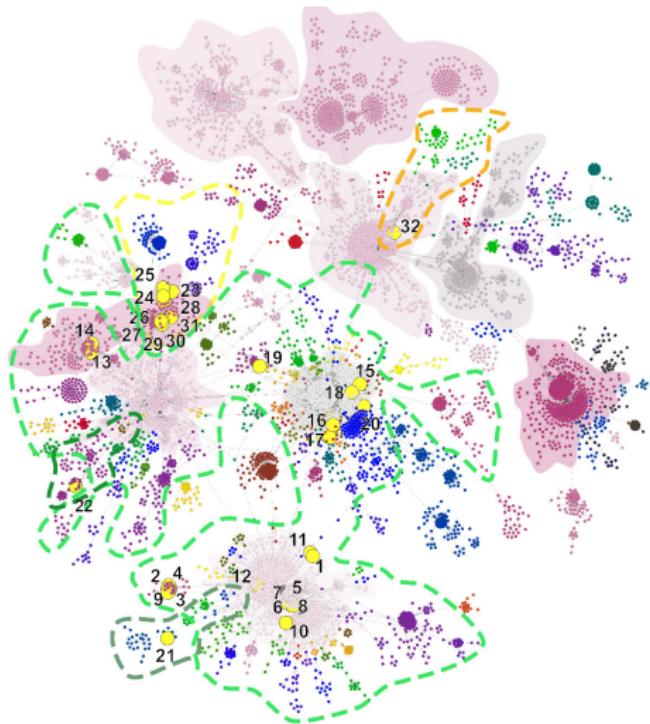


Figure 1. Genetic network analysis of 7864 SARS-CoV-2 complete genomic sequences. Hungarian strains are indicated with numbered yellow dots—numbers referring to Table 1. The nine major clades are represented by a solid color. Genetic lineages are marked with colored dotted lines, where green lines are bordering B 1, B 1.1 and B 1.11; yellow and orange lines mark B 1.5 and B 3, respectively.

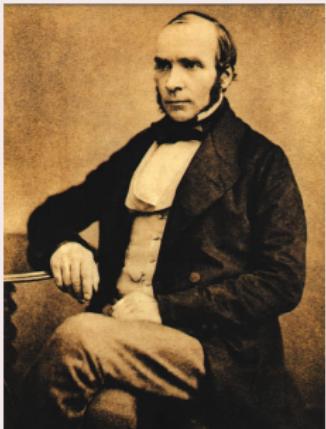
Az epidemiológia emberi és állati *populációkon* belül a betegségek megelőzésével és visszaszorításával foglalkozik. A betegségek előfordulását, kialakulását befolyásoló tényezők és a betegség közötti kapcsolatokat vizsgálja.

Fontos rámutatni arra, hogy az epidemiológia nem kizárolag fertőző betegségekkel foglalkozik, hanem kóroktól függetlenül az egészséggel kapcsolatos események populáción belüli előfordulásával, az azt meghatározó tényezőkkel. Az állatorvosi epidemiológia ezenkívül magába foglalja egyéb, az állatok egészségével kapcsolatos tényezők (különösen a termelékenység) vizsgálatát, elemzését is.

A hazai és külföldi szakirodalomban is találkozhatunk az epizootiológia kifejezéssel, azonban hosszas nemzetközi vita (1994) után ma már ezt a kifejezést nem használják.

- Az egészségkárosodás oksági modelljei
- A betegség állatpopulációkban való előfordulásának számszerűsítése
- Túlélési vizsgálatok
- Diagnosztikai tesztek eredményeinek statisztikai értelmezése
- Kockázatelemzés
- EBVM
- Állatbetegségek földrajzi elterjedtségének elemzése
- Betegség kitörési, terjedési modellek
- Mintaszám becslése
- Monitoring és surveillance rendszerek (MOSS)





John Snow
1813-1858



<https://www.youtube.com/watch?v=2GhQ7AYHLr4>

Az epidemiológia a betegségek előfordulását, kialakulását befolyásoló tényezők és a betegség közötti kapcsolatokat vizsgálja.

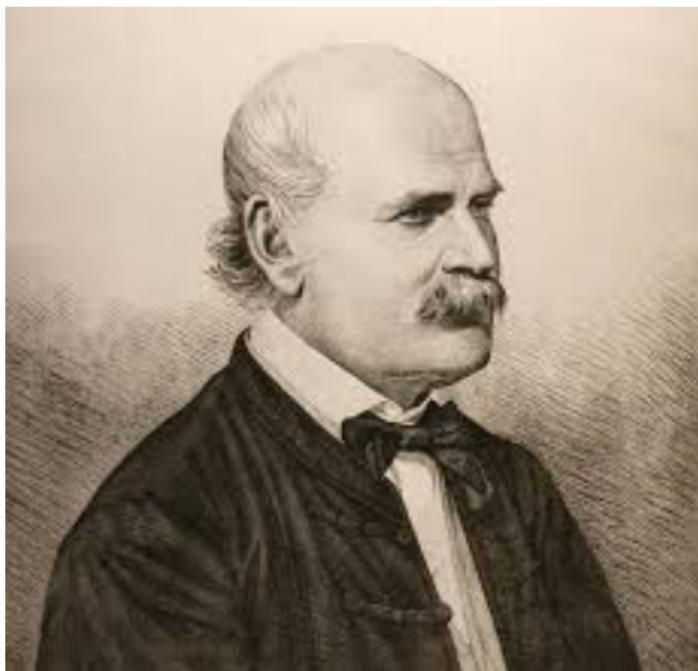
A természettudományban elsődlegesen az a cél, hogy azonosítsuk az okokat, amelyekkel magyarázható valamely természeti jelenség.

Az okság tanulmányozása az ok (hatás) és okozat közötti kapcsolattal foglalkozik, mind a természettudomány mind a filozófia területén.

együttállás (association) vagy ok és okozat (causality)?

„Fortis imaginatio generat casum”
Michel de Montaigne (1533–1592)

A serological survey of 213 randomly chosen dairy farm residents in the Manawatu showed that 66 (34%) of the people who milked cows had leptospiral titres $\leq 1:24$ by the Microscopic Agglutination Test. Forty-eight (72.7%) of these people had titres to hardjo, while 29 (43.9%) had titres to pomona. Dual hardjo/pomona titres occurred in 12 people. Ballum and Copenhageni accounted for 8% of the titres found. Women milkers and farm residents who did not milk were all serologically negative. A third of the seropositive milkers had a history of clinical leptospirosis. Other factors which significantly correlated with leptospiral titres included the time spent in the dairy shed during milking, the **wearing of shorts**, the keeping of pigs for sale, and the number of years the individual had been working on a dairy farm. The type of milking shed and the size of the herd were interrelated and both showed strong trends towards a correlation with serological prevalence.



Semmelweis Ignác Fülöp (1818–1865)

- 1847: klórmeszes kézmosás elrendelése
- 1879: Pasteur gyermekágyi lázas mintából *streptococcusokat mutat ki**
- okság? együttállás? hatékonyság

Lev 13,4:

„Ha azonban csak fénylő fehér folt van a bőrön, de az nem mélyebb, mint a többi test, s a szőr színe a régi, akkor zárassa el őt a pap hét napig.”

A magas virulenciájú kórokozók okságának vizsgálatában a Koch-féle posztulátumok (1884) kielégítő modellként szolgált.

Az organizmus oksági szerepet játszik, ha

- 1 a betegség minden esetében jelen van
- 2 nem fordul elő más betegségekben, mint véletlen (fortuitous) vagy nem patogén parazita
- 3 izolálható a beteg állatból, színtenyészet hozható létre belőle, amit ismételten leolthatunk és más állatokban ugyanazt a betegséget idézhetjük elő vele

A multifaktoriális betegségek esetén az oksági kapcsolatok feltárásában használhatatlan.

Az első tíz halálozási ok változása

Év	Sorrend	Betegség	Részarány (%)
1860	1	tuberkulózis	19.8
	2	hasmenés, bélgyulladás	15.0
	3	kolera	6.4
	4	pneumonia/influenza/bronchitis	6.1
	5	csecsemőkori halálozás	5.9
	6	diphtheria	2.7
		vérhas	2.7
		stroke	2.7
	9	skarlát	2.5
	10	nephritis	2.4

Az első tíz halálozási ok változása

Év	Sorrend	Betegség	Részarány (%)
1900	1	pneumonia/influenza/bronchitis	14.4
	2	tuberkulózis	11.3
	3	hasmenés, bélgyulladás	8.1
	4	szívbetegségek	8.0
	5	nephritis	4.7
	6	balesetek	4.5
	7	stroke	4.2
		korai csecsemőkori betegségek	4.2
	9	daganatok	3.7
	10	diphtheria	2.3

Az első tíz halálozási ok változása

Év	Sorrend	Betegség	Részarány (%)
1970	1	szívbetegségek	38.3
	2	daganatok	17.2
	3	stroke	10.8
	4	pneumonia/influenza/bronchitis	3.6
	5	balesetek (motorbalesetek kivételével), öngyilkosság	3.1
	6	motorbalesetek	2.8
	7	korai csecsemőkori betegségek	2.3
	8	cukorbetegség	2.0
	9	arteriosclerosis	1.7
	10	cirrhosis	1.6

Hill-féle kritériumok (1965) oksági kapcsolat értékeléséhez:

① a kapcsolat erőssége

- erősebb kapcsolat nagyobb **valószínűséggel** jelenthet okságot
- a gyengébb nem jelenti azt, hogy nem lehet ok-okozati kapcsolat

② konzisztencia

- mások eredményei is ugyanazt a kapcsolatot jelzik?

③ specifikusság

- egy kitettség egy betegséget okoz: egyértelmű az okság
- ha nem így van, akkor sem kizáró

④ az események időbeli sorrendisége

⑤ biológiai gradiens

- ha dózis-válasz kapcsolatot tudunk kimutatni a tényező és a betegség között, akkor megemelkedik annak a **valószínűsége**, hogy a tényező oksági

⑥ a meglévő ismeretekkel való összeegyeztethetőség

- biológiai mechanizmus

⑦ kísérteletes bizonyíték

⑧ analógia

Evans-féle posztulátumok (1976)

- 1 a beteg egyedek részaránya szignifikánsan magasabb kell, hogy legyen azok között az állatok között, amelyek ki voltak téve a feltételezett kóroknak, mint azok között, akik nem voltak kitéve
 - 2 a feltételezett oknak való kitettség gyakoribb a betegséget mutatók között, mint a betegséget nem mutatók között (feltesszük, hogy a többi kockázati tényező azonos szintű a két csoportban)
 - 3 prospektív vizsgálatok során az új megbetegedések száma szignifikánsan magasabb a feltételezett kóroknak kitett csoportban, mint a nem kitettek között
 - 4 időben a megbetegedés a feltételezett oknak való kitettség után következik be, a kettő között eltelt lappangási idő alakja haranggörbe
-

Evans-féle posztulátumok (1976)

- 5 a gazda választartományának (ennyétől súlyosig) követnie kell a feltételezett oknak való kitettség mértékét, egy biológiaileg logikus skálán
 - 6 a gazda mérhető válaszának (pl. ellenanyag) szabályosan kell megjelennie a feltételezett oknak való kitettséget követően, azokban, akik a kitettség előtt nem adtak ilyen választ; illetve ilyen válasz nem jelentkezhet azokban, akik nem voltak kitéve a feltételezett kockázati tényezőnek
 - 7 *kísérletesen* gyakrabban lehet előidézni a betegséget azokban az egyedekben, amelyek ki voltak téve a feltételezett kóroknak, mint azokban, akik nem (kísérletesen laboratóriumban vagy kontrollált természetes kitettség)
-

Evans-féle posztulátumok (1976)

- 8 a feltételezett kórok eltávolításának vagy módosításának (pl. a hiányos táplálás módosítása) csökkentenie kell a betegség előfordulásának gyakoriságát
 - 9 prevencióval vagy a gazda válaszának módosításával (pl. immunizálás) csökkennie kell, vagy el kell tűnnie a feltételezett kóroknak való kitettség mellett megjelenő esetek számának
 - 10 minden kapcsolatnak és összefüggésnek biológiaileg és epidemiológiailag hihetőnek kell lennie
-

No. 4356 April 25, 1953

NATURE

737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

- ¹ Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
² Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Suppl.*, **5**, 285 (1949).
³ Von Arx, W. S., Woods Hole Papers in Phys. Oceanogr. Meteorol., **11** (3) (1956).
⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1906).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment further.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis as diagram 1. We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to

This figure is purely diagrammatic. The legend
the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain roughly resembles Furberg's model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration

is a residue on each chain every 3·4 Å. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric form (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are : adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally^{3,4} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data⁶ on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more recent results. Some of these are given in the following communication. We will give some of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

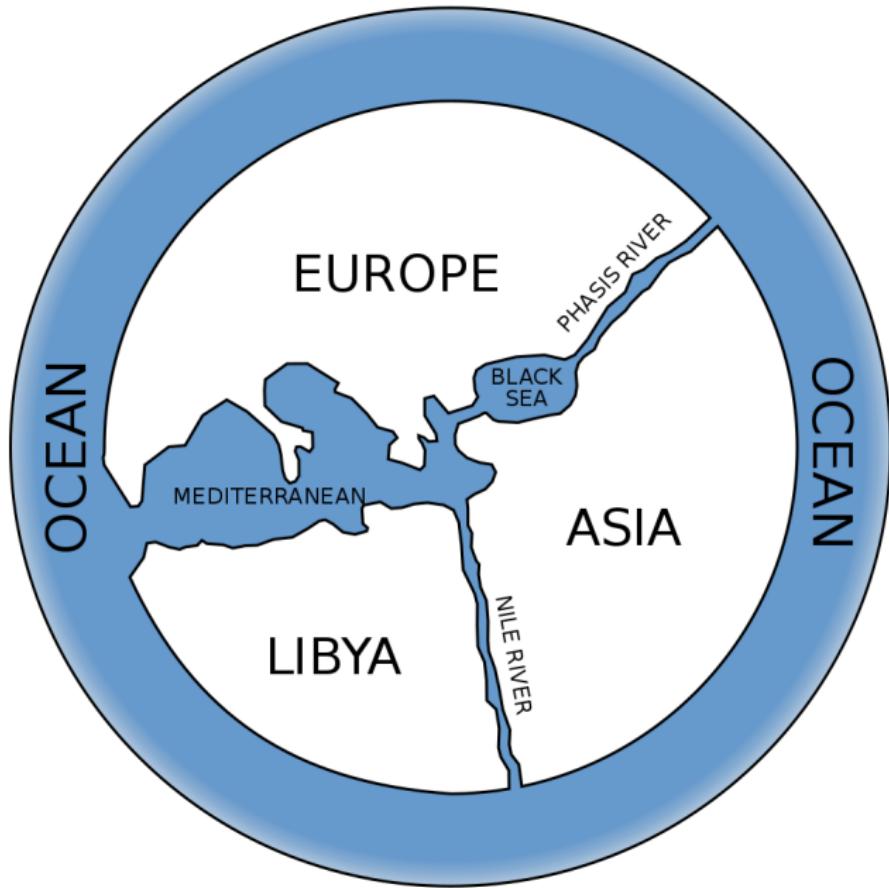
We are much indebted to Dr. Jerry Donohue for



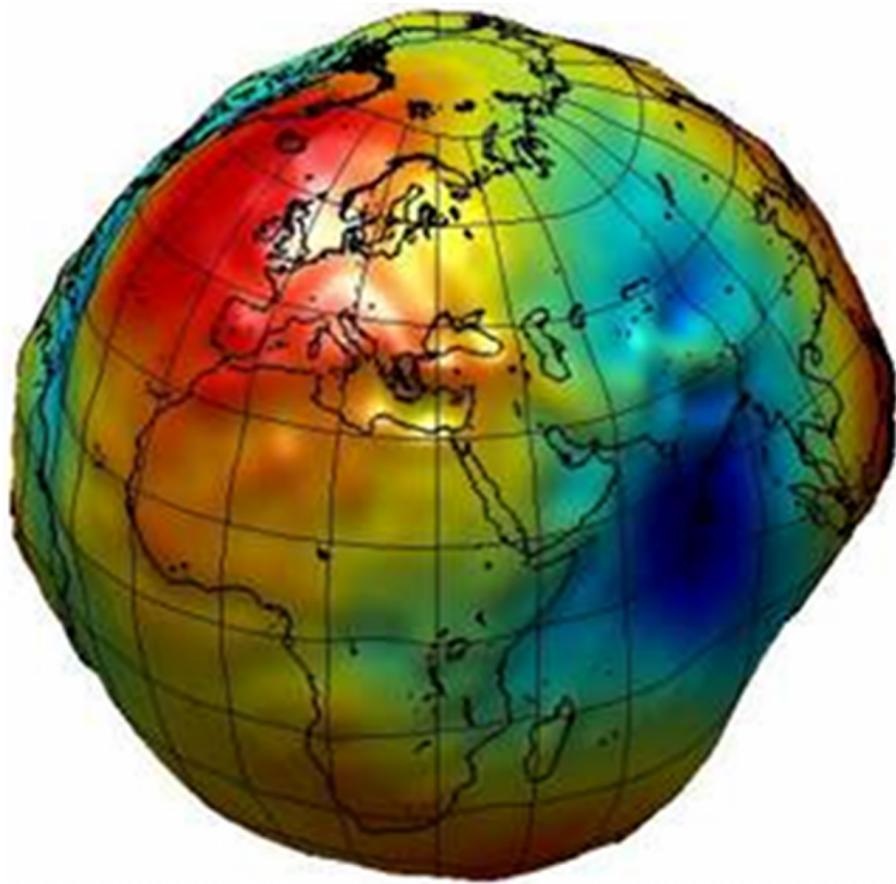
*"All models are wrong
but some are useful"*

George E. P. Box

1919–2013

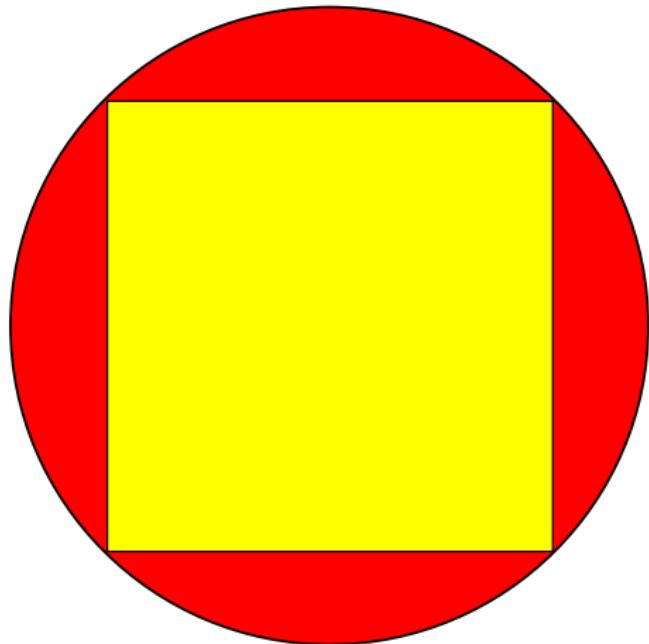






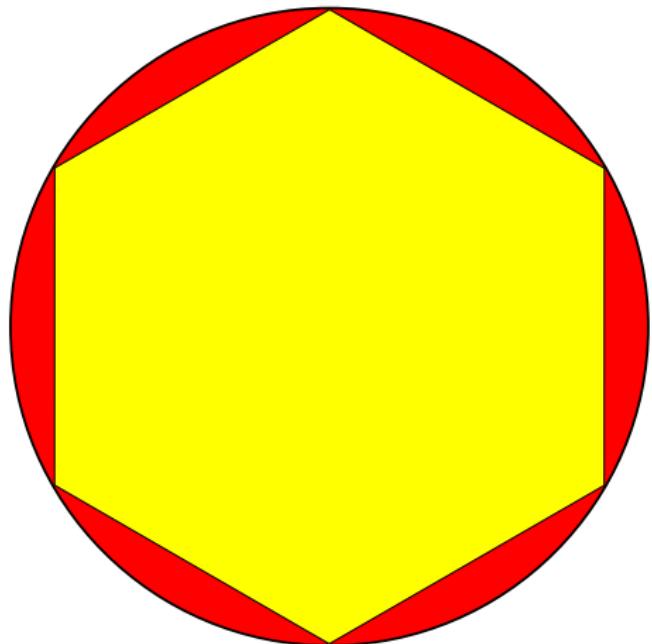


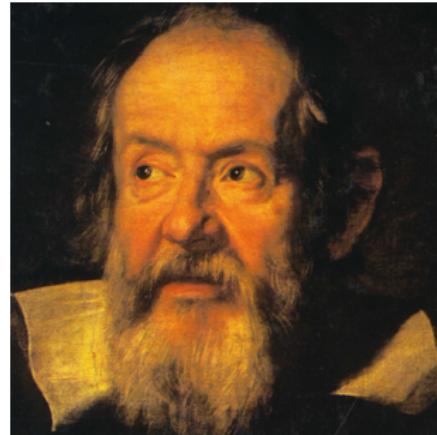
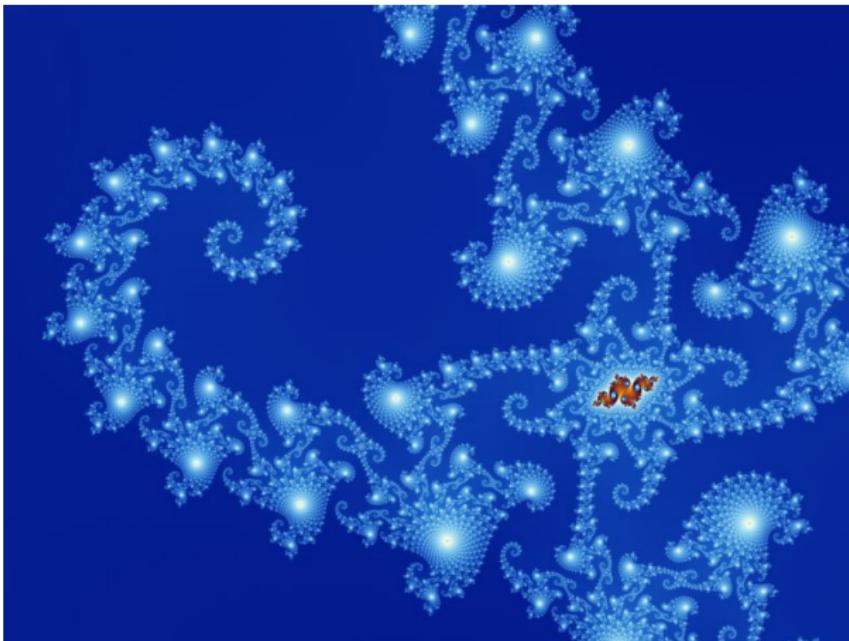
Nicolaus Cusanus
1401–1464





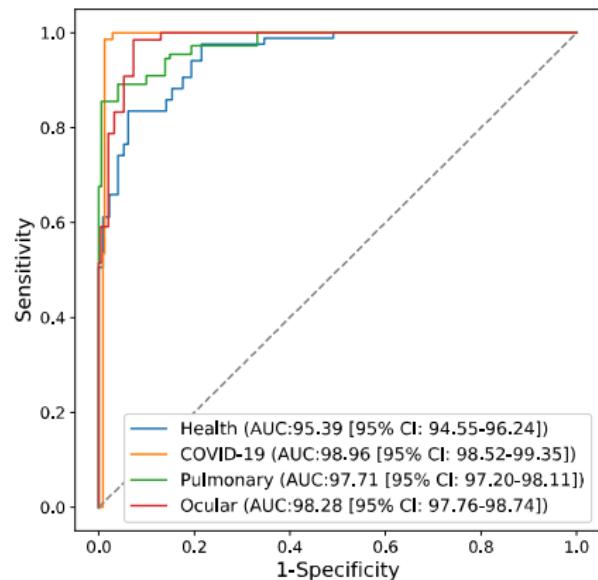
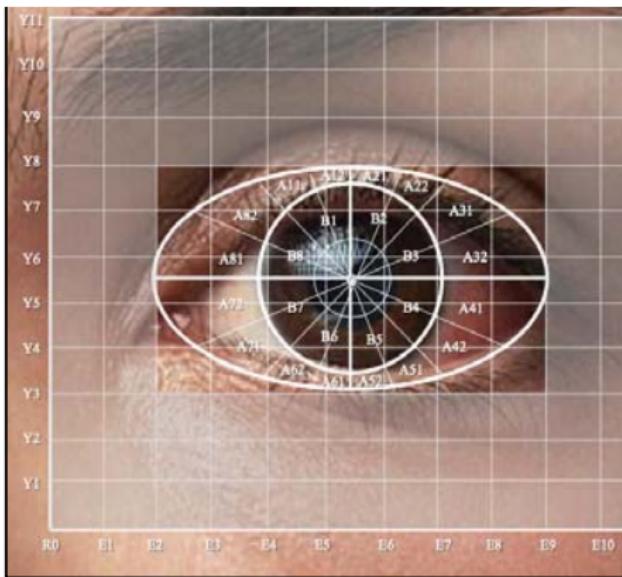
Nicolaus Cusanus
1401–1464

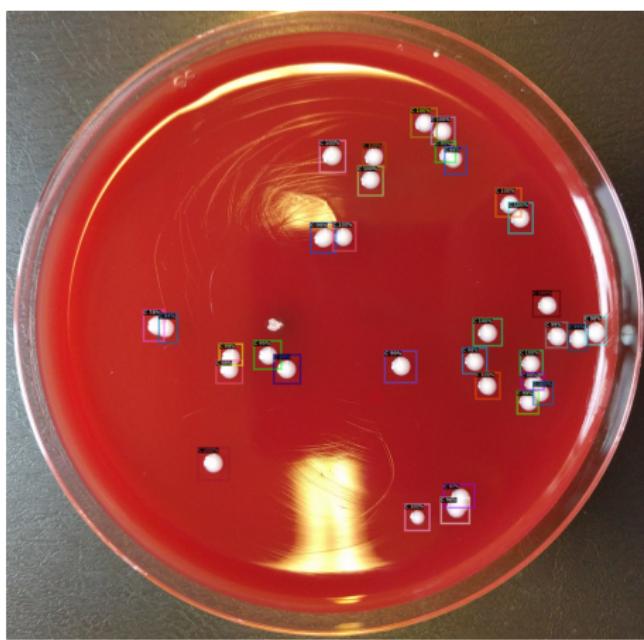
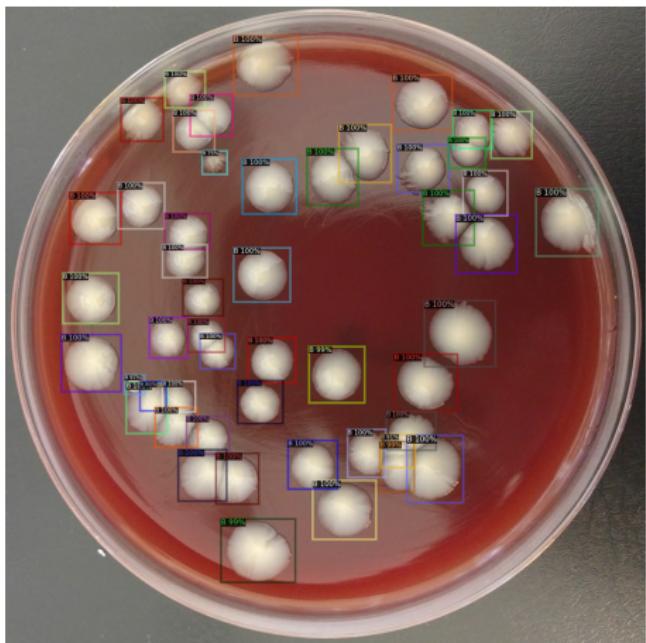




Galileo Galilei
1564–1642

$$Z_{n+1} = z_n^2 + C$$





- Bastos, M. L., G. Tavaziva, S. K. Abidi, J. R. Campbell, L.-P. Haraoui, J. C. Johnston, Z. Lan, S. Law, E. MacLean, A. Trajman, et al. (2020). Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. *BMJ* 370.
- Del Valle, D. M., S. Kim-Schulze, H.-H. Huang, N. D. Beckmann, S. Nirenberg, B. Wang, Y. Lavin, T. H. Swartz, D. Madduri, A. Stock, et al. (2020). An inflammatory cytokine signature predicts covid-19 severity and survival. *Nature medicine*, 1–8.
- Dohoo, I., W. Martin, and H. Stryhn (2002). *Veterinary Epidemiologic Research* (2nd ed.). Charlottetown, Prince Edward Island, Canada: VER Inc.
- Fu, Y., F. Li, W. Wang, H. Tang, X. Qian, M. Gu, and X. Xue (2020). A new screening method for covid-19 based on ocular feature recognition by machine learning tools. *medRxiv*.
- Glasziou, P., A. Burls, and R. Gilbert (2008). Evidence based medicine and the medical curriculum. *BMJ (Clinical Research Ed.)* 337(7672), 704–705.
- Greenhalgh, T. (2020, 06). Will COVID-19 be evidence-based medicine's nemesis? *PLOS Medicine* 17(6), 1–4.
- Kemenesi, G., S. Zeghbib, B. A. Somogyi, G. E. Tóth, K. Bányai, N. Solymosi, P. M. Szabó, I. Szabó, Á. Bálint, P. Urbán, R. Herczeg, A. Gyenessei, Á. Nagy, C. I. Pereszlenyi, G. C. Babinszky, G. Dudás, G. Terhes, V. Zöldi, R. Lovas, S. Tenczer, L. Kornya, and F. Jakab (2020). Multiple SARS-CoV-2 introductions shaped the early outbreak in Central Eastern Europe: comparing Hungarian data to a worldwide sequence data-matrix. *bioRxiv*.
- Mackintosh, C., L. M. Schollum, R. Harris, D. Blackmore, A. Willis, N. Cook, and J. Stoke (1980). Epidemiology of leptospirosis in dairy farm workers in the Manawatu Part I: A cross-sectional serological survey and associated occupational factors. *New Zealand Veterinary Journal* 28, 245–250.
- Mehra, M. R., S. S. Desai, S. Kuy, T. D. Henry, and A. N. Patel (2020). Cardiovascular disease, drug therapy, and mortality in covid-19. *New England Journal of Medicine*.
- Noordhuizen, J. P. T. M., K. Frankena, M. Thrusfield, and E. A. M. Graat (2001). *Application of Quantitative Methods in Veterinary Epidemiology*. Wageningen, The Netherland: Wageningen Pers.
- Pfeiffer, D. (2002). Veterinary epidemiology: An introduction. ww3.panaftosa.org.br/Comp/MAPA/431857.pdf.
- Pfeiffer, D. (2010). *Veterinary Epidemiology: An Introduction*. Oxford, UK: Wiley.
- Pollán, M., B. Pérez-Gómez, R. Pastor-Barriuso, J. Oteo, M. A. Hernán, M. Pérez-Olmeda, J. L. Sanmartín, A. Fernández-García, I. Cruz, N. F. de Larrea, et al. (2020). Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *The Lancet* 396(10250), 535–544.
- Smith, R. D. (2005). *Veterinary Clinical Epidemiology: From Patient to Population* (3rd ed.). Boca Raton, Florida, USA: CRC Press.
- Thrusfield, M., R. Christley, H. Brown, P. J. Diggle, N. French, K. Howe, L. Kelly, A. O'Connor, J. Sargeant, and H. Wood (2018). *Veterinary Epidemiology* (4th ed.). Oxford, UK: Wiley.