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Researching research

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Dan Ryan, COIOS

22 July 2020

Structure

- Background
- History and challenges
- Evidence and bias
- ‘Emergency epidemiology’
- Final comments

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Background

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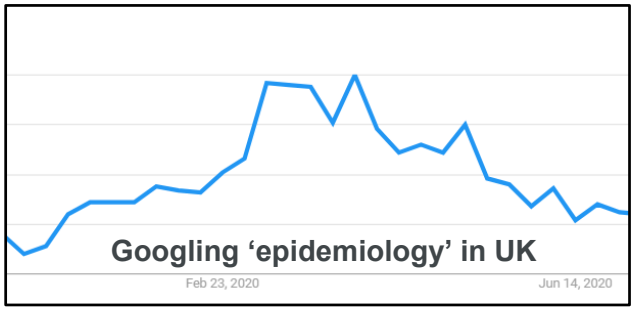
Everyone's an epidemiologist these days …

OED | Oxford English Dictionary
The definitive record of the English language

Home > Updates to the OED > New words list April 2020

New words list April 2020



- Covid-19, n.: "An acute respiratory illness in humans caused by a coronavirus, which is capable of producing severe symptoms and death, esp. in the elderly and…"
- infodemic, n.: "A proliferation of diverse, often unsubstantiated information relating to a crisis, controversy, or event, which disseminates rapidly and…"
- R0, n.: "The average number of cases of an infectious disease arising by transmission from a single infected individual, in a population that has not…"
- to flatten the curve (at CURVE n.): "(*Medicine, spec. Epidemiology*) : to take measures designed to reduce the rate at which infection spreads during an epidemic, with the aim of lowering the peak daily number of new cases and extending the period over which new cases occur."

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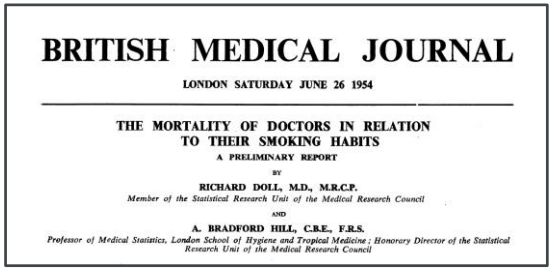
History

- Snow on Cholera
  - 1854
  - 120 deaths
  - Water pump

- Doll and Hill
  - 1954
  - Smoking



BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 26 1954

THE MORTALITY OF DOCTORS IN RELATION TO THEIR SMOKING HABITS

A PRELIMINARY REPORT

BY

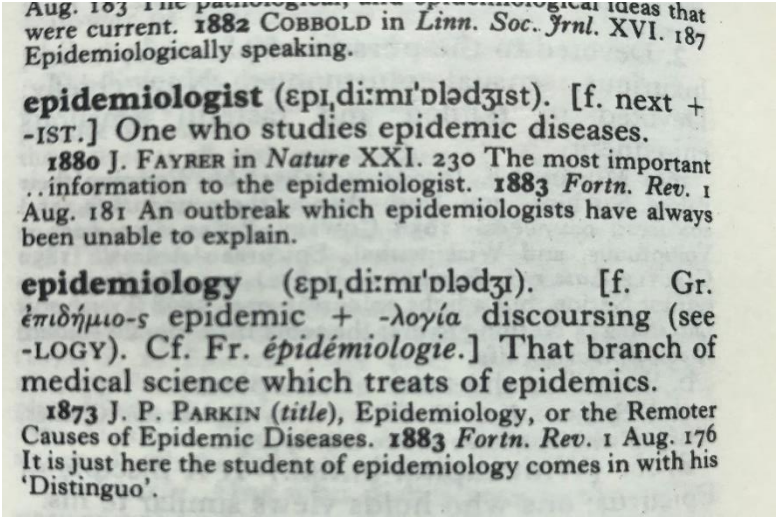
RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., F.R.S.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council



were current. **1882** COBBOLD in *Linn. Soc. Jrnl.* XVI. 187 Epidemiologically speaking.

epidemiologist (ɛpɪˌdiːmɪˈɒlədʒɪst). [f. next + -IST.] One who studies epidemic diseases.

1880 J. FAYRER in *Nature* XXI. 230 The most important ..information to the epidemiologist. **1883** *Fortn. Rev.* 1 Aug. 181 An outbreak which epidemiologists have always been unable to explain.

epidemiology (ɛpɪˌdiːmɪˈɒlədʒɪ). [f. Gr. *ἐπιδήμιο-ς* epidemic + *-λογία* discoursing (see -LOGY). Cf. Fr. *épidémiologie*.] That branch of medical science which treats of epidemics.

1873 J. P. PARKIN (*title*), Epidemiology, or the Remoter Causes of Epidemic Diseases. **1883** *Fortn. Rev.* 1 Aug. 176 It is just here the student of epidemiology comes in with his 'Distinguo'.

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Bradford Hill Criteria for Causality

- **Strength (effect size):** A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
- **Consistency (reproducibility):** Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
- **Specificity:** Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation.
- **Temporality:** The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
- **Biological gradient (ie dose response relationship):** Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect (like a catalyst). (Or an inverse proportion may act.)
- **Plausibility:** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
- **Consistency:** … between epidemiological and laboratory findings increases the likelihood of an effect (eg clinical findings)
- **Experiment:** Do preventive actions taken on the basis of an assumed causal association alter the outcomes?
- **Analogy:** The effect of similar factors?

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50 years later …

- We can look back on massive advances in areas such as smoking, and the start of granular data collection to allow longitudinal studies
- Great increases in knowledge through RCTs
- But …
  - *'Much of the scientific literature, perhaps half, may simply be untrue." … "afflicted by studies with small sample sizes, tiny effects … an obsession for pursuing fashionable trends of dubious importance, science has taken a turn toward darkness.'* (Richard Horton, Editor, The Lancet April 11, 2015)
  - *'It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians.'* (Dr. Marcia Angell, former Editor of the New England Journal of Medicine)
  - *'In modern research, false findings may be the majority or even the vast majority of published research claims.'* (John Ionannidis, 'Why Most Published Research Findings Are False')

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What went wrong?

- Diminishing returns
  - We started with smoking, now we're looking at broccoli
  - All-cause mortality risk factors of the order of x2 – now we have x[1.2] for specific causes
  - Problem of polypharmacy – some people may gain from fewer, not more, drugs
- Trust
  - Pharmaceutical companies are 'companies' not charities
  - $38 billion of 'big pharma' penalties since 2000, with the largest four (Pfizer, GSK, Johnson & Johnson, Merck) averaging over $4 billion each ('Violation Tracker' website)
- Misleading results
  - Hormone Replacement Therapy – first major (observational) study indicated a 40% reduction in cardiovascular risk … years later, an RCT shows +30% risk (with the first study distorted by 'healthy behaviour' bias)

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Evidence and bias

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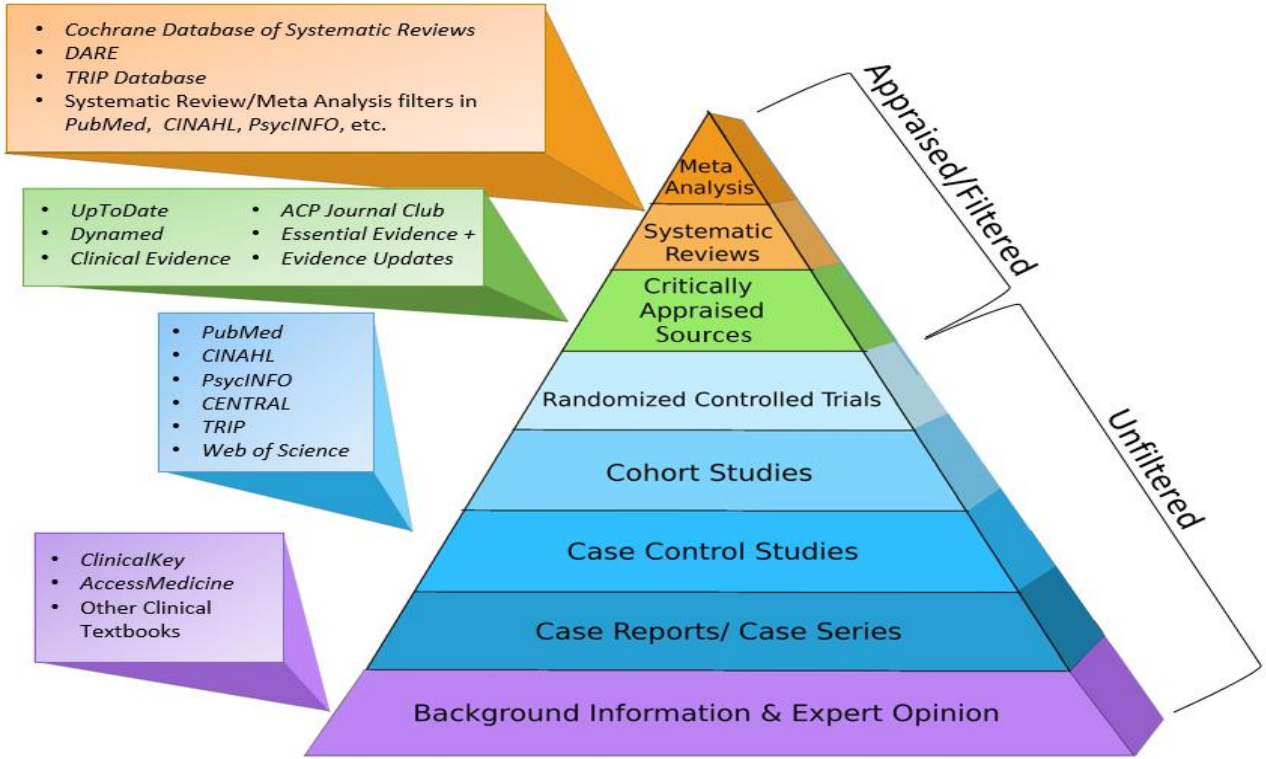
Scaling the hierarchy of evidence



Source: Andy Puro (2014)

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Steering a course through biased waters

- Observer bias
  - gathering data through a human filter, improved by training and reflection
- Lost subjects to follow-up
  - losing those we most wanted to understand – Abraham Wald and bullet holes
- Distorting effects of sponsorship
  - lack of perceived commercial benefit restricts ambition & size of trials
- Heavy hand of peer review
  - tempering conclusions
  - rejecting findings

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‘Emergency epidemiology’

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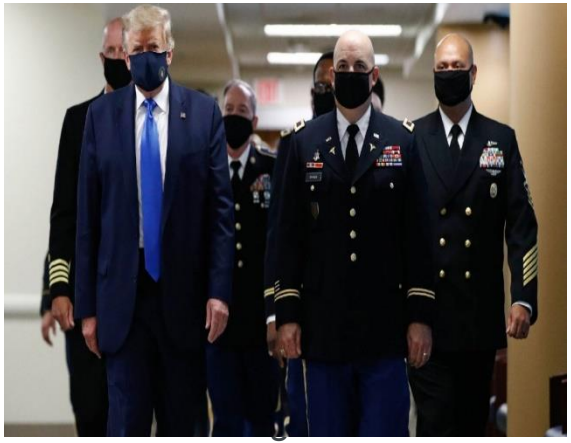
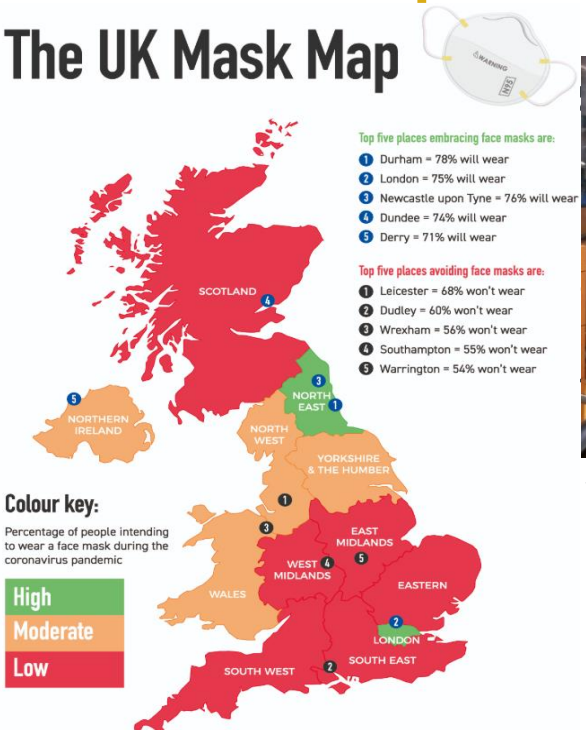
Pandemics, face masks and the precautionary principle



- 24 July: Face coverings mandatory in UK shops and supermarkets



Source: Missouri hair salon reopening

Sources: BMJ, N95 Mask Company (Survey of 2,000 adults 1-3 May)

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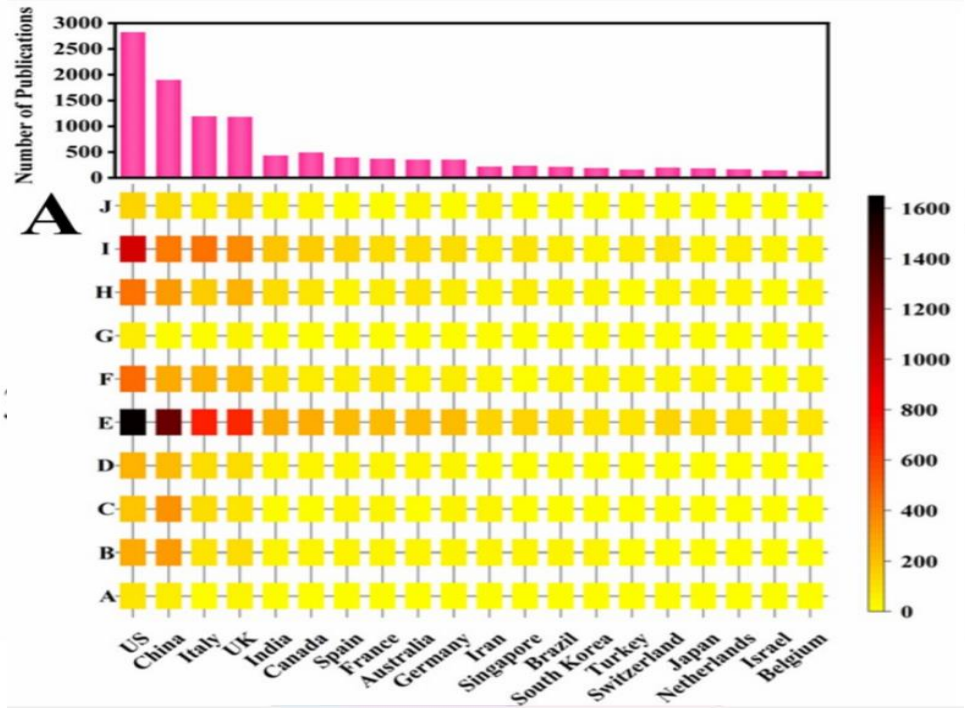
Challenges to peer review in the time of COVID-19



A.Origin & gene sequencing
B.Epidemiological characteristics
C.Clinical characteristics
D.Pathology & molecular biology
E.Diagnostic method
F.Pharmaceutical treatment
G.Vaccine development
H.Prevention and control strategy
I.Study targeting specific population
J.Review

Source: Global pattern of COVID-19 research

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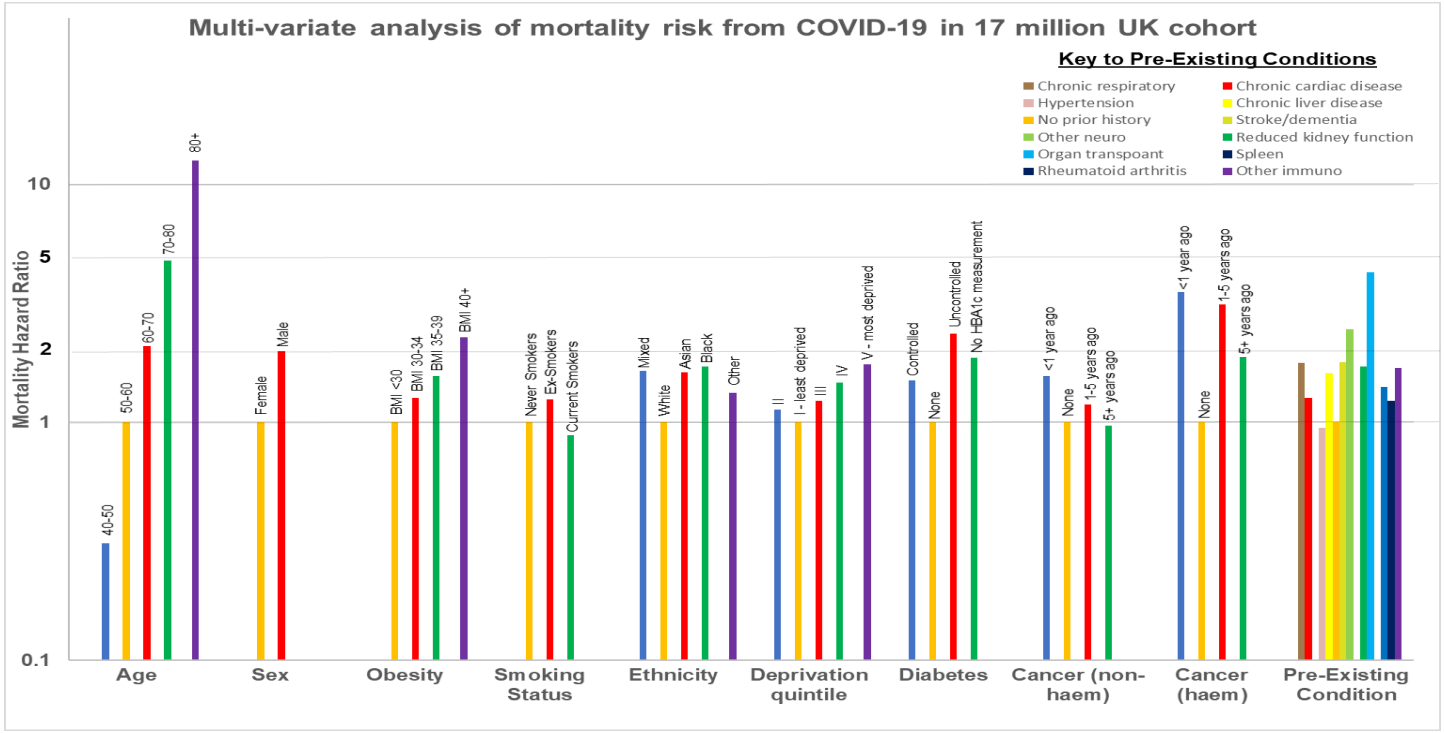
Unlocking power of multivariate analyses with eHR



Source: Opensafely.org

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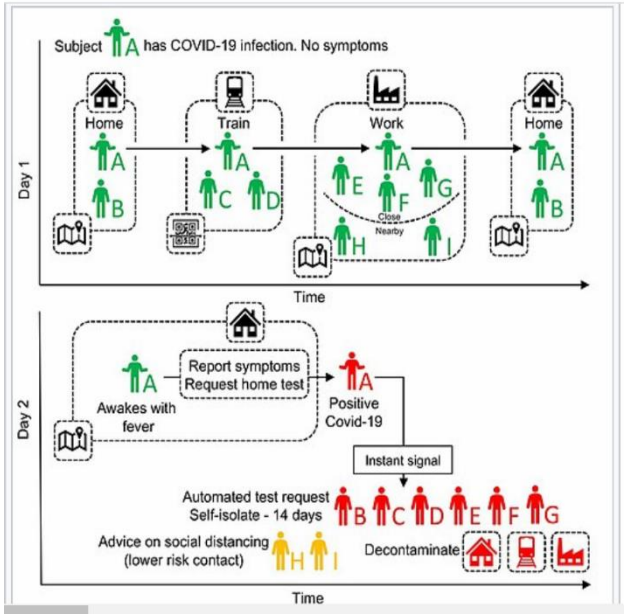
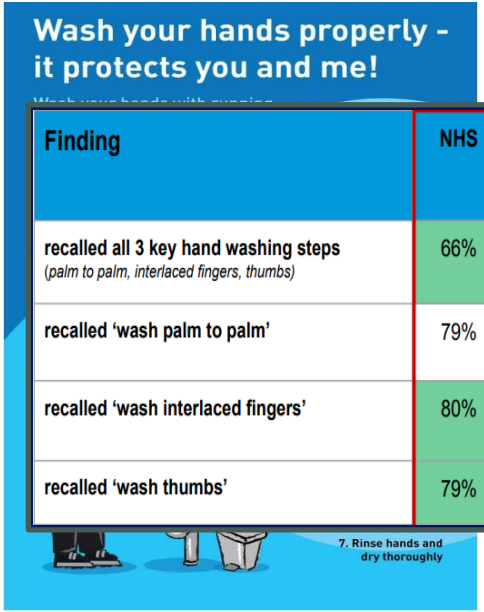
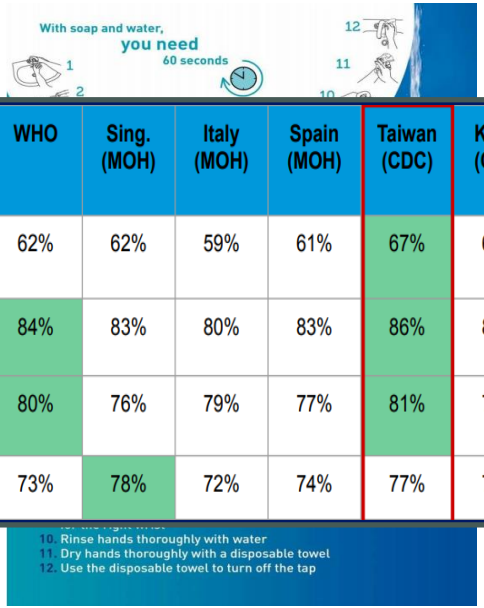
Modern paradigms of research – digital apps & behavioural trials



Taiwan



Italy



Finding	NHS	WHO	Sing. (MOH)	Italy (MOH)	Spain (MOH)	Taiwan (CDC)	Korea (CDC)
recalled all 3 key hand washing steps *(palm to palm, interlaced fingers, thumbs)*	66%	62%	62%	59%	61%	67%	61%
recalled 'wash palm to palm'	79%	84%	83%	80%	83%	86%	80%
recalled 'wash interlaced fingers'	80%	80%	76%	79%	77%	81%	76%
recalled 'wash thumbs'	79%	73%	78%	72%	74%	77%	77%

Source: COVID-19 apps

Source: Behavioural Insights Team (23 March)

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Future hopes of a vaccine

Rapidly expanding pipeline of vaccines at different stages in development

11	6	2	18	49	17	15	11	1
DNA	Inactive	Live weaken	Non-rep viral vector	Protein	Replicating viral vector	RNA	VLP	Unknown

Vaccine	Company	Phase	Country
ChAd0x1-nCoV-19	Oxford Univ/AstraZeneca	III	UK
Vero-inactivated	Wuhan Institute	III	CHN
PicoVacc	SinoVac	III	CHN
Ad5-nCoV	CanSino Bio	II	CHN
mRNA-1273	Moderna	II	USA
LV-SMENP-DC	Shenzhen GIMI	I/II	CHN
BNT162	Pfizer/BioNTech	I/II	GER, USA

Sources: Artis Ventures, Coalition for Epidemic Preparedness Innovation

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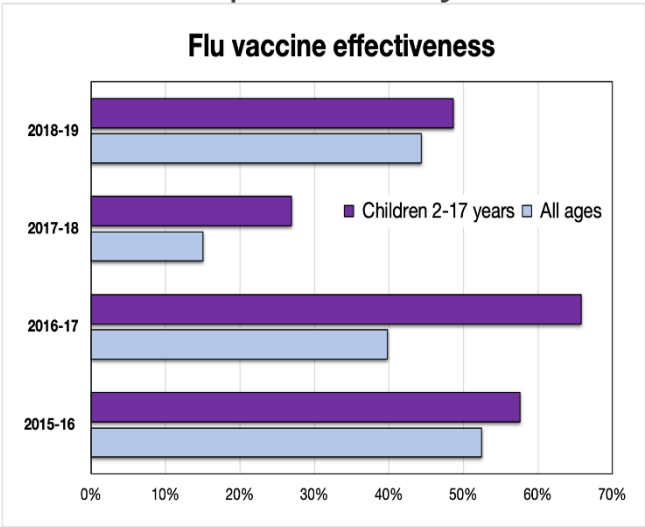
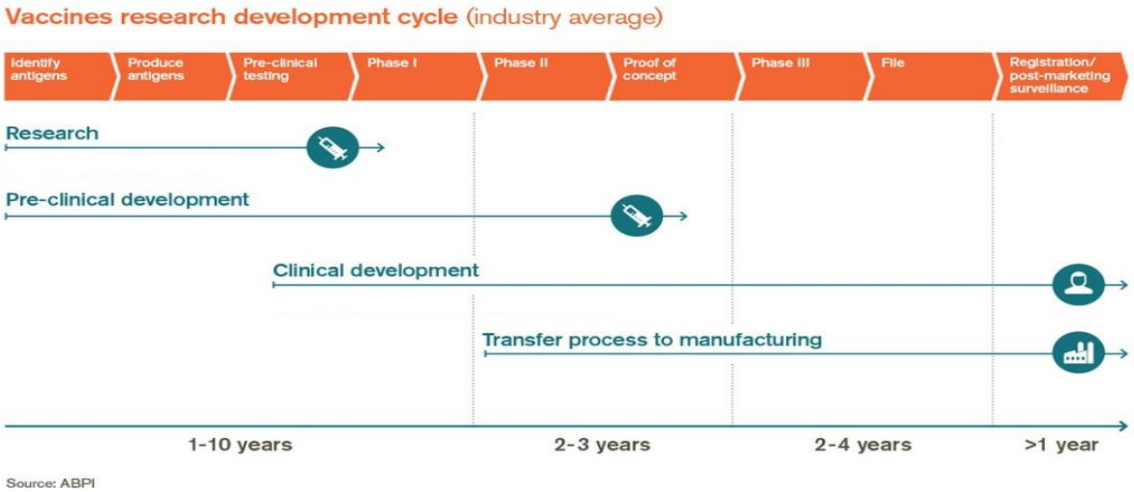
Operation Warp Speed & vaccine development

Balancing target dates with vaccine testing & effectiveness
Development in 1 year would require dramatic acceleration of all stages





Sources: Association of British Pharmaceutical Industry, Public Health England

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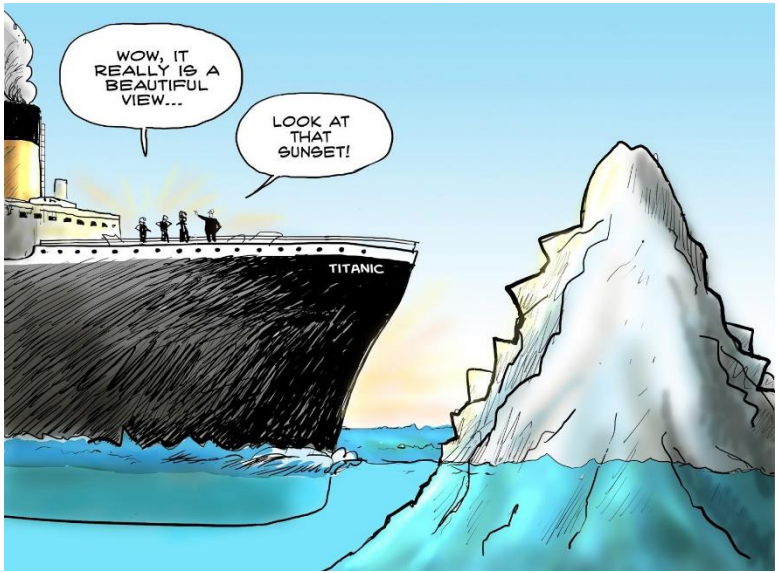
Evidence-based medicine after COVID-19

- Patients must be able to enter relevant and appropriate clinical trials.
- Encourage use of routinely collected, anonymised data to support epidemiological studies.
- Focus on prospective, multicentre, well-designed studies looking to assess causation/effectiveness.
- Design studies for deployment in future pandemics.



Source: Mark Hill for Bayer Pharmaceutical

Source: Evidence-based medicine and COVID-19: what to believe and what to change

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Final comments

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Final thoughts – by way of a ‘sense-check’ list

- **Impact** – what is the all-cause mortality impact if the results are correct? Many findings published recently imply negligible I.e. impact. Many studies also look at endpoints other than morbidity/mortality.
- **Data bias** – how might bias be present in data selection, or in the operation of confounding factors? Data bias can be present in almost undetectable ways; for instance, operating a pre-trial period to determine if any individuals suffer side-effects from the medication.
- **Commercial bias** – given the penalty sums noted, pharma companies can clearly adopt questionable approaches to justify the promulgation of drugs that may earn them in the order of $100 billions.
- **Association or causation** – very few study types allow us to safely infer causation, although in a typical insurance underwriting context *association may be sufficient*
- **Biological plausibility** – are the results plausible regarding the underlying biological process and, similarly, are they consistent with clinical evidence and the wider question of fitting an evolutionary perspective on what ‘works’?

Many of these points, just as many of the Bradford Hill criteria, are useful in broader ‘big data’ analytical contexts. Do findings tie in with day-to-day reality (so biological plausibility above becomes the old question, ‘Would an underwriter believe this result?’).

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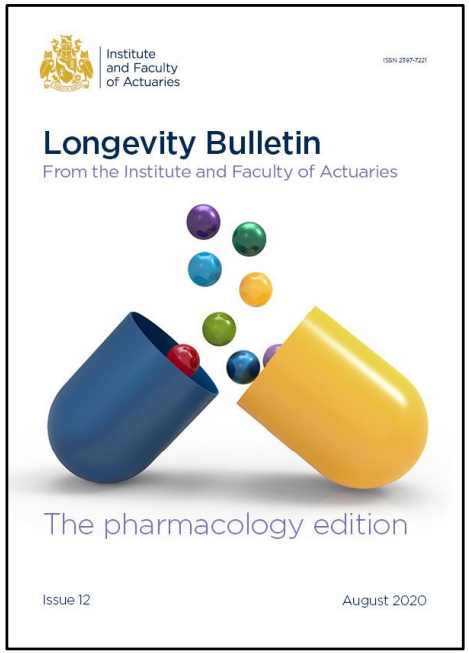
Further detail in the forthcoming Longevity Bulletin



- ‘Researching research’
- Opioids in the UK, *Dr Chris Martin*
- Pharma and diabetes, *Nicola Oliver*
- Polypharmacy, *Dr Malcolm Kendrick*
- Opioids in the US, *Magali Barbieri*
- CMI update

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Questions

Comments

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