Dr Murray May **18 August 2023**

Submission on exposure draft of the Communications Legislation Amendment (Combatting Misinformation and Disinformation) Bill 2023

I submit the following on the above draft Bill, and have strong concerns that it has the potential to silence dissenting views and experts, and act merely to entrench government narratives, which may in themselves constitute misinformation. No one government or agency has a monopoly on truth. Our perception of truth evolves over time with experience. Thus:

1. Who decides what constitutes 'misinformation'/' disinformation? (Their qualifications, experience, ties with industry)
2. To whom and what products will it apply?
3. How will the government determine what constitutes'misinformation'/'disinformation'?
4. How will the government monitor developments in diverse areas to update its understanding of information/disinformation in the future?
5. How will the government communicate to all Australians (of all ages, ethnicities, education levels and abilities) what they can and can't say in the future?

I provide two examples of how this Bill could exert a strong censorship role, even embedding out of date misinformation from the government itself in the process.

Example 1 ACMA is a statutory body overseeing telecommunications licensing. ACMA personnel are not scientists, academics, researchers or medical professionals. ACMA staff are not qualified to act as arbitrator on the issues of RF/EMR exposures and health. Instead, ACMA defers to ARPANSA, which uses the guidelines of the industry linked non-government body ICNIRP.

This means that on EMR issues, ACMA by definition subscribes to the view that only thermal effects are relevant for making decisions on electromagnetic radiation and health. However, there is now a considerable body of scientific opinion and peer reviewed scientific literature on the non-thermal impacts of electromagnetic radiation (both to human health and the environment), including concerns related to 5G.

I attach an example paper (Davis et al. Wireless technologies, nonionizing electromagnetic fields and children: Identifying and reducing health risks, *Curr Probl Pediatr Adolesc Health Care* 2023; 53:101374), though many have been published in 2023, and the 286 references in the Davis paper show the literature is significant. ARPANSA seeks to ignore or contradict such analysis. Further, I received a reply from the Department of Infrastructure that my communications to the Minister alerting her to newly published literature, will not receive a response. In other words, the Minister and Department apparently want to bury their

heads in the sand in relation to the developing paradigm and remain attached to an out of date one.

The consequences of this approach are no longer academic either. I provide clips from a website below on a US case that asks the Federal Communications Commission to do its homework properly.

https://ehtrust.org/press-conference-eht-et-al-v-fcc-landmark-case-on-wireless-5g-safety/

In an historic decision, the U.S. Court of Appeals for the District of Columbia Circuit judged in favour of environmental health groups and petitioners on Aug. 13, 2021, finding the Federal Communications Commission (FCC) violated the Administrative Procedure Act and failed to respond to comments on environmental harm.

The court ruled that the decision by the FCC to retain its 1996 safety limits for human exposure to wireless radiation was “arbitrary and capricious” and held that the FCC failed to respond to “record evidence that exposure to RF radiation at levels below the Commission’s current limits may cause negative health effects unrelated to cancer.”

Further, the agency demonstrated “a complete failure to respond to comments concerning environmental harm caused by RF radiation.” The court found the FCC ignored numerous organisations, scientists and medical doctors who called on them to update limits. Human exposure guidelines for wireless radiation were last set in 1996.

The Court found that the FCC did not provide evidence of properly examining evidence such as:

1. impacts of long-term wireless exposure
2. impacts on children
3. the testimony of persons injured by wireless radiation
4. impacts on the developing brain
5. impacts on the reproductive system
6. impacts on wildlife and the environment.

The Court specifically ordered the FCC to provide a reasoned explanation for these issues:

- the impacts of wireless radiation on children
- the health implications of long-term exposure to RF radiation
- the ubiquity of wireless devices and the technological developments since the FCC last updated its guidelines.
- the cell phone radiation emission test methods that use heat measurements and allow a space between the phone and body.
- the impacts of wireless radiation on the environment.

Example 2 Information provided by credible scientists and leading physicians demonstrated that mRNA vaccines used during the Covid pandemic were neither safe nor effective, as claimed by the government. Could and would the planned Misinformation Bill be used to censor such information because it brings to light embarrassing information and contradicts the prevailing government narrative?

Thus Wiseman et al. (see attached paper) in a submission to the US FDA found that:

There is inadequate evidence for safety of booster doses amidst mounting concerns for the first two doses:

- Significant safety concerns need to be addressed for the Covid-19 vaccines as presently used, and with the use of booster doses.
- We show intense safety signals for the Covid-19 vaccines compared with influenza vaccines with 176 times the number of deaths/person vaccinated reported in VAERS.
- To account for any stimulated reporting, compared with H1N1 vaccines where stimulated reporting was suspected, this ratio is still high at 35.
- Although classical disproportionality analysis is inadequate and superseded by methods that normalize for actual doses administered or people vaccinated, we nonetheless detected strong age-dependent signals for deaths, serious events coagulopathy and myocardial infarction.

More recent published papers have only reinforced the above concerns about vaccine damage considerably above the rate of previous vaccines e.g. J. Fraiman, J. Erviti, M. Jones et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine* 40 (2022) 5798–5805. This paper is attached.

Another paper from medical experts attached (Bardosh K, *et al*. *BMJ Global Health* 2022;7:e008684. doi:10.1136/bmjgh-2022-008684) notes that mandatory COVID-19 vaccine policies used around the world during the COVID-19 pandemic to increase vaccination rates provoked considerable social and political resistance. They suggest this has had unintended harmful consequences and may not be ethical, scientifically justified, and effective.

Trust in government has been considerably eroded as adverse and sometimes very serious vaccine damage has been observed in personal networks, in spite of government assurances that mRNA vaccines were “safe and effective”. The AZ vaccine has also been withdrawn for use in Australia because of concerns about clotting effects.

Docket No. FDA-2021-N-0965

Written comments submitted to:
Vaccines and Related Biological Products Advisory Committee (VRBPAC) September 17, 2021 Meeting

Booster Doses for Pfizer-BioNtech Vaccine

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Summary

- There is inadequate evidence for safety of booster doses amidst mounting concerns for first two doses
- Significant safety concerns need to be addressed for the Covid-19 vaccines as presently used, and with the use of booster doses.
- We show intense safety signals for the Covid-19 vaccines compared with influenza vaccines with 176 times the number of deaths/person vaccinated reported in VAERS.
- To account for any stimulated reporting, compared with H1N1 vaccines where stimulated reporting was suspected, this ratio is still high at 35.
- Although classical disproportionality analysis is inadequate and superseded by methods that normalize for actual doses administered or people vaccinated, we nonetheless detected strong age-dependent signals for deaths, serios events coagulopathy and myocardial infarction.
- We identified three separate pools of vaccine associated deaths, totaling 45,000-147,000 deaths.
  - Non C19 deaths under reported in VAERS 20,400-62,500
  - C19 deaths occulting in vaccinated 25,000-85,000
  - An unknown number of deaths in non-vaccinated contributed by transmission from vaccinated.
  - These figures should be placed in the context of the upper estimate of 140,000 lives saved due to the vaccines (to May 2021)(1)
  - The benefits of vaccination should be considered in light of resistant strains, waning immunity(2) and development of natural immunity(3).
  - Unresolved safety questions for pregnant mothers must be resolved.
- Products must be regulated as gene therapy products, with appropriate long term follow up for autoimmune diseases, cancers etc.
- Significant short and Long term health issues require the ***Recognition of short and long term vaccine -related effects as a major public health issue.*** To concretize recognition of, and to spur action to avert and confront this potential public health crisis, we propose the term:

Post Covid Vaccine Syndrome – pCoVS

A syndrome occurring after injection of antigen-inducing, gene therapy vaccines to SARS-Cov-2 virus. The syndrome is currently understood to manifest variously as cardiac, vascular, hematological, musculoskeletal, intestinal, respiratory or neurologic symptoms of unknown long-term significance, in addition to effects on gestation. Manifestations of the syndrome may be mediated by the spike protein antigen induced by the delivered nucleic acids, the nucleic acids themselves, or vaccine adjuvants. As more data become available, subsets and longer-term consequences of pCoVS may become apparent, requiring revision of this definition. Sub-categories may be designated by suffix for example:

- We propose the establishment of an ICD10 code for pCoVS, and an mechanism to fund research into pCoVS.

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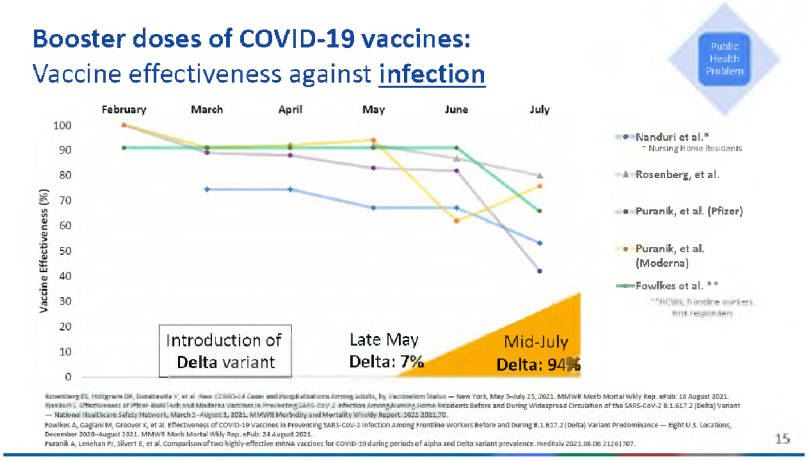
1. Introduction: Waning or Reduced Effectiveness of Covid-19 Vaccines

Globally[1] (9/13/21) around 5.5 billion doses of Covid-19 vaccines have been administered, mostly pursuant to Emergency Use Authorization (USA) or equivalent status. At a recent (8/30/21) meeting of CDC's Advisory Committee on Immunization Practices (ACIP), evidence was presented by CDC staff(4) regarding reduced effectiveness of the Covid-19 vaccines, in some scenarios as low as 42% for the Pfizer-BioNTech Covid-19 vaccine.(5)



Slide 15 from (4)

Whether this decline is due to waning immunity over time, or reduced effectiveness against the relatively new delta variant, is not fully understood. Whatever the case, the decline has prompted the *"the Pfizer-BioNTech supplemental Biologics*

[1] covid19.who.int/

License Application for COMIRNATY for administration of a third dose, or "booster" dose, of the COVID-19 vaccine, in individuals 16 years of age and older" which is the subject of the discussion at this meeting.[2]

The purpose of this document is to document concerns that we believe should be considered by VRBPAC in its deliberations. Our concerns fall into five categories:

- **Regulatory:** Which legally distinct product is being discussed and under what regulatory authorization type and product classification?
- **Transparency and public trust:** The issuance of a BLA without a public meeting or comment, apparent withholding of evidence prior to CDC's ACIP recent vote to recommend the Pfizer vaccine, and announcement of ancillary safety studies suggest a lack of transparency that erodes trust in public health officials. Such erosion, we suggest, is a major driver in vaccine hesitancy.
- **Safety:** Since there are mounting and unresolved safety concerns for the two-dose regime, and a paucity of data on the booster dose, how can FDA assure the public of the safety of additional doses?
- **Efficacy:** Concerns for bias and sources of confounding
- **Policy towards repurposed drugs** must be re-examined due to a change in risk-benefit analysis.

Please note that this document extends our previous comments discussed in written submissions (6,7) for the recent ACIP meeting of CDC (8/30/21) as well as in an Op-Ed article of a respected clinical trials web site.(8)

2. Regulatory Concerns

2.1. Which legally distinct product is under consideration and under which authorization type?

According to the FDA's announcement of this meeting, the topic under discussion is *"the Pfizer-BioNTech supplemental Biologics License Application for COMIRNATY."* (footnote 2)

Prior to August 23rd, an EUA (Emergency Use Authorization) was in place for a product known as the "Pfizer-BioNTech COVID-19 Vaccine" as referred to in a revised EUA letter of May 10.(9)

On August 23rd 2021, in a letter to Pfizer, Inc., FDA disclosed the existence of two legally distinct [footnote 8 in (10)] vaccine products:

- Pfizer-BioNTech COVID-19 Vaccine: this product was to remain under EUA.
- COMIRNATY (COVID-19 Vaccine, mRNA) – a BLA was issued on August 23rd for this product(11) to BioNTech Manufacturing GmbH.

According to that letter, these two products can be used "interchangeably" but have "certain differences that do not impact safety or effectiveness"

According to FDA, since the COMIRNATY product, as a practical matter is not available, the EUA for the Pfizer-BioNTech product would remain in place. However, as popularly understood, for example in this Reuter's news headline[3] the *"Pfizer-BioNTech COVID-19 vaccine gains full U.S. regulatory approval."*

Accordingly, the announced topic for this meeting

"the Pfizer-BioNTech supplemental Biologics License Application for COMIRNATY."

is at best unclear. The only company of record with a product called COMIRNATY with a BLA to which a supplement could be added is BioNTech Manufacturing GmbH. Pfizer-BioNTech has a legally distinct product referred to in official documents (10) as *"Pfizer-BioNTech COVID-19 Vaccine."*

Will the agency clarify:

- For which legally distinct product is an approval of a booster dose being considered?
- If FDA intends to supplement BLA approval for booster doses for a product (COMIRNATY) that is not available, but not authorize their emergency use under an EUA, how can this be of any help whatsoever?

[2] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-17-2021-meeting-announcement#event-materials

[3] www.reuters.com/business/healthcare-pharmaceuticals/us-fda-grants-full-approval-pfizer-biontech-covid-19-vaccine-2021-08-23/

- If two legally distinct products exist, why is it only possible in VAERS (9/13/21) to report events for the Pfizer-BioNTech product and not for the BioNTech (ie COMIRNATY) product?
- What are the "certain differences that do not impact safety or effectiveness" between the EYa and BLA products?(10)
- What are the legal ramifications of having two legally distinct products in terms of:
    - Operation of different regulatory standards to conduct safety monitoring, reporting of advesrse events, or adherence to other regulatory requirements?
    - Liability of manufacturers or health providers for injuries resulting from the use of vaccines?
    - Ability of patients to bring actions under various statues for vaccine-related injuries?
    - Ability of patients to obtain compensation under the National Vaccine Injury Compensation (or similar) Program?[4]
    - Other ramifications?

2.2. Vaccines or Gene Therapy Products? Regulatory and Safety Consequences

2.2.1. Regulatory Classification

Although these Covid-19 agents fall under FDA's definition of vaccines and vaccine-associated products,[5]

> *"products, regardless of their composition or method of manufacture, intended to induce or enhance a specific immune response to prevent or treat a disease or condition, or to enhance the activity of other therapeutic interventions."*

they differ significantly from the classical vaccine consisting of an inactivated or attenuated pathogen in two major respects. Firstly, rather than an immune response being elicited by injected antigen, it is elicited by antigen (the SARS-Cov2 spike protein), whose within-subject biosynthesis is induced by mRNA or DNA deployed by the vaccine.

Secondly, these vaccines also meet FDA's definition of gene therapy products.[6]

> (emphasis added) *"Human gene therapy/gene transfer is **the administration of nucleic acids**, viruses, or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or **altered in vivo by gene therapy products administered directly to the recipient**."* A similar expanded definition is given in FDA's Guidance on Long Term Follow-Up After Administration of Human Gene Therapy Products.(12)

Moderna, Inc., the maker of another mRNA Covid-19 vaccine, acknowledged in their 2Q2020 SEC filing(13)[7] thus *"Currently, mRNA is considered a gene therapy product by the FDA."* These vaccines might be more appropriately be described as "Gene Therapy Vaccines" (GTV).

Consistent with the FDA June 2020 guidance(14) on the development of vaccines for Covid-19, Pfizer,[8] Moderna[9] and Johnson & Johnson,[10] declared their intent in their requests for EUA status to follow study subjects for up to 36 months. Parenthetically, an additional concern has arisen in the unblinding of at least some of the clinical trials, thus preventing full assessment of safety as previously declared.(15)

Even this 36-month follow-up period is inadequate for two reasons. Firstly, although the sorts of events anticipated by FDA and CDC are of relatively early onset, the duration or prognosis for a number of them is unknown. Secondly, since these

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[4] www.hrsa.gov/vaccine-compensation/index.html

[5] www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research

[6] *www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research*

[7] Moderna's 2Q2020 SEC filing is dated August 6 2020, and states that the phase 1 study began March 16, 2020, with the phase 2 study being fully enrolled by July 8, 2020. Enrollment for the phase 3 study began July 27, 2020, as also reflected in for clinicaltrials.gov. Each phase would have been cleared by FDA. The start date given in clinicaltrials.gov for Pfizer's trial was April 29 2020 and for J&J Sept 7 2020.

[8] https://www.fda.gov/media/144245/download

[9] https://www.fda.gov/media/144434/download

[10] https://www.fda.gov/media/146219/download

agents are also Gene Therapy products, much longer surveillance is warranted for delayed malignant, neurologic, autoimmune, hematologic, other disorders or effects on the genome or gene expression, as advised in FDA in its guidance document "Long Term Follow-up After Administration of Human Gene Therapy (GT) products."(12) The length of monitoring advised by FDA may be (emphasis added) "***as long as 15 years*** *following exposure to the investigational GT product, specifying that the LTFU observation should include a minimum of five years of annual examinations, followed by ten years of annual queries of study subjects, either in person or by questionnaire."*

Accordingly, the designation of these vaccines as Gene Therapy products is not merely a semantic nicety; rather it has regulatory consequences in terms of long term follow up manufacturers should be required to conduct. No reference to these FDA guidance documents on long term follow up for gene therapy products (12) was made in FDA's guidance on development of Covid-19 vaccines(14), nor in the EUA briefing documents provided by Pfizer, Moderna and Johnson & Johnson.

Will FDA provide an explanation as to why the provisions relating to Gene Therapy products have not been incorporated into the risk-benefit analysis of these vaccines, or the types and durations of studies it has required of these products?

Will FDA explain why the classification of these products as Gene Therapy Products, evinced by Moderna's disclosure in August 2020, has been all but ignored in terms of the types and durations of studies it has required of these products?

2.2.2. Will long term studies and cancer be performed?

THE BLA for COMIRNATY acknowledges LONG term myocardial issues with a 5 year follow up in a required post-marketing study consistent with the lower range for LTFU for Gene Therapy Products.

As contemplated in the FDA Gene Therapy Guidance document?(12), there appear to be no plans for FDA or CDC to collect other long-term data (or require studies) on autoimmune disease, cancer and other disorders This is particularly concerning as the package insert(16) states that *"COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility*." Neither in the in the BLA Approval letter,(11) or Summary Basis for Regulatory Approval(17) is there a POST MARKETING REQUIREMENT to conduct carcinogenicity, genotoxicity or male fertility.

A number of Covid vaccine surveillance systems operate under the aegis of FDA[11] and/or CDC.[12] CDC lists six follow-up studies below.

Study	Final analysis	Interim (short term)
COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants	March 2023	July 2021 Jan 2022
Mortality and Vaccination with COVID-19 Vaccines	April 2024	Oct 2021 Apr 2022
COVID-19 Vaccine safety, Spontaneous Abortion (SAB) and Stillbirth in the VSD	April 2023	Monthly surveilance
COVID-19 Vaccine-Mediated Enhanced Disease (VMED) and Vaccine Effectiveness in the VSD	Q1 2023	Q2-3 2021 Q2-3 2022
VSD Tree-Based Data Mining	Aug 2023	
VSD RCA Protocol version	Approx 2023	Ongoing

While it is appropriate to conduct these sorts of studies, it is noteworthy that the concerns expressed in the objectives for a number of these studies are not reflective of the extensive media campaign to promote vaccination and its safety. We will discuss specific details of some of these studies in the sections below. In our opinion this contravenes the principles of obtaining informed consent for medical treatment.

2.2.3. Economic cost of long term follow up of Gene Therapy products – who will pay?

Understanding the concerns that this distinction reveals has other significant long-term consequences. Given that these Gene Therapy Vaccines (GTV) have been used on what may fairly be termed an experimental basis, **every** GTV recipient

[11] www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance

[12] www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html

may be subject to, or even entitled to long-term monitoring, as well as early intervention of delayed events. Assuming, conservatively, an annual cost of $500 per person, and based on an estimated (8/29/21) 204 million of Americans having received at least one GTV dose, this amounts to an annual cost of some $102 billion, just for the USA. This figure is comparable to the 2020 budgets or revenues of NIH ($42b), Pfizer ($42b), Johnson & Johnson ($83b) or Facebook ($86b) and eclipses estimates of between $25 billion and $35 billion for the global Covid-19 vaccine market. Considering the approximately 4.5 billion GTV recipients around the world, this annual global cost, before any treatment or indirect costs, will approach trillions of dollars. Who will absorb this cost? Government? Medicare? Medicaid? The manufacturers of the Gene Therapy Vaccines? Private insurers? Patients?

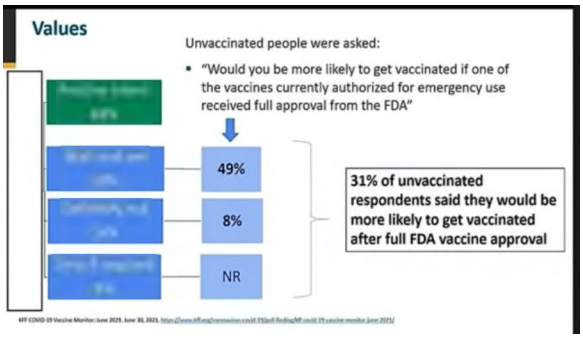
3. Transparency and Public Trust Concerns

Much is being made about vaccine hesitancy, particularly that attributed to "*misinformation*." Allow us to suggest that the problem is not unjustified mistrust in the vaccines. It is justified mistrust of public health officials fueled by contraventions of the best traditions of American democracy such as:

- FDA's issuance of a BLA without a public meeting or comment.
- The apparent withholding of evidence of waning immunity prior to CDC's ACIP recent vote to recommend the Pfizer vaccine.(8)
- The lack of transparency within NIH regarding the formulation of their treatment guidelines.
- The effective admission by CDC that the primary driver to issue a full FDA approval for any one of the Covid-19 vaccines, along with a CDC.ACIP recommendation was vaccine hesitancy,(18) rather than the accumulation of sufficient evidence for safety and efficacy. CDC referenced a survey which asked unvaccinated people:

  *"Would you be more likely to get vaccinated **if one** of the vaccines currently authorized for emergency use received full approval from the FDA"* (emphasis added). *Of these, "31% of unvaccinated respondents said they would be more likely to get vaccinated after full FDA vaccine approval," meaning - OF ANY OF THE VACCINES.*

  The presentation suggested that: *"Vaccination may be more acceptable to stakeholders under full FDA approval and standard ACIP recommendation."*



Acceptability

- Vaccination with Pfizer-BioNTech COVID-19 vaccine was already highly acceptable to stakeholders under FDA emergency use authorization and ACIP interim recommendation
- Vaccination may be more acceptable to stakeholders under full FDA approval and standard ACIP recommendation

Another source of mistrust is the inconsistent use of standards of evidence. The use of observational or non-peer reviewed (preprinted) studies by proponents of re-purposed drugs has been heavily criticized by public health officials as well as the media, who have insisted on evidence from large RCTs that have undergone peer review. It was with some wonder that observational and non-peer reviewed studies were included in one of the key analyses provided to support ACIP's recommendation. In one analysis (slide 19) from a presentation[13] analyzing vaccine efficacy, 17 observational studies, including 7 non-peer-reviewed, were employed. The presenter concurred with a remark by one of the discussants that there was close agreement between the observational studies and the RCT. We welcome the example that CDC has set to allow for these sorts of analyses to inform other decisions relating to the pandemic and public health.

There is also mistrust due to the demonization and censorship of the many medical professionals and scientists who have raised concerns about these vaccines and have advocated for the use of repurposed drugs. These workers are from across the political spectrum who are not only proponents of classical type vaccines, but also proponents of gene therapy products

[13] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf

that employ DNA or mRNA technologies to treat cancer and other heretofore incurable diseases. As with all new technologies, safety is paramount, and we assert that until proven otherwise, the risk-benefit balance demands a re-assessment of the justification for the continued use of these Gene Therapy Vaccines (GTVs), especially as booster doses are now being considered.

In addition to concerns related to the gene therapy nature of these products there are concerns about the toxicology of the spike protein antigen, the adjuvants themselves as well as downstream consequences at the gene or mRNA level. Importantly, inexpensive, safe and effective prevention and treatment based on repurposed drugs are readily available. (19)

The contentions that our motivations are rooted elsewhere or that allegedly politically motivated advocacy for use of repurposed drugs in Covid-19 has spewed misinformation fueling vaccine hesitancy is a perversion of the truth as such advocacy is subject to heavy censorship within social media, the peer reviewed scientific literature and in professional contexts. At a time when unity against Covid-19 is sorely needed, this demonization serves to increase divisiveness and political polarization. This demonization erodes patients' fundamental rights to choose whether or not to undergo any sort of medical treatment, and erodes physicians' freedom to practice medicine, by prescribing treatments they believe to be in the best interests of their patients.

Governments, public health agencies and the medical community must address the safety consequences of these vaccines and at the same time make fundamental corrections to heretofore employed approaches to Covid-19 and the suppression of legitimate scientific debate.

Can FDA and this committee provide an assurance that it will do everything in its power to defuse the current toxic atmosphere that is stifling scientific discussion?

4. Ongoing and Unresolved Safety Concerns for Covid-19 vaccines

The discussion on booster doses in the August 30 meeting of CDC's ACIP recognized the challenges in producing reliable data that could support the use of booster doses. It was unclear that there was any significant body of data available to address either safety of efficacy of booster doses. Limited data on efficacy have now emerged. One recent study(20) suggested that waning or reduced immunity can be restored with a booster dose, but this is only partial, and is at best, according to the study, temporary.

Before considering the safety of a third vaccine dose, it is entirely appropriate to discuss the ongoing concerns regarding the first two doses.

4.1. Safety signal analysis of events from VAERS

4.1.1. Insensitivity of Disproportionality Signal Analysis (DSA) used to detect safety signals

Several methods have been proposed to detect safety signals related to medical products, specifically from databases of spontaneous adverse event reports, such as VAERS. In general, these methods do not infer causality, merely they provide a signal for further investigation. To mitigate a number of statistical and informational challenges, methods involving Disproportionality Signal Analysis (DSA) have been devised, such as the use of the Proportional Reporting Ratio (PRR) or other Bayesian or data mining techniques. The VAERS team have indicated that these sorts of methods should be employed to detect safety signals for the Covid-19 vaccines.(21) Although DSA is a useful tool in pharmacovigilance (PhV) it has known limitations. A paper authored by scientists from Astra-Zeneca, Pfizer, as well as British and European regulators stated: *"Thus, the quantitative data in spontaneous reporting systems, while being useful in detecting new signals of drug-event associations, are not easily interpretable in terms of clinical impact" (22)* The authors further stated *"calculation of PRRs from spontaneous reporting databases should not replace nor delay the performance of formal epidemiological studies,"*

DSA uses the total number of reports reported for a particular drug as a surrogate denominator to estimate the incidence of a particular event in the population, to be compared with other drugs in the same class. Although methods exist to partially compensate for masking of a particular event by other events, as well as non-independence of events, the output from these techniques remains that of a signal which provides no estimate of **epidemiological or clinical impact.** This problem is compounded in the case of drugs where, even if the number of prescriptions written are known, detail as to actual usage, dose, length of treatment and so on may not be.

In the case of the Covid-19 vaccines, the primary reasons for employing a surrogate denominator do not pertain: individual doses are usually fixed, the number of doses given is fixed, with mostly uniform dose intervals. Lastly, the number of doses administered as well as the number of persons receiving those doses, is known from CDC tracking systems. We note that presentations made at CDC's ACIP meeting on August 30 largely relied on event incidence rates expressed as the number of events per 100,000 (or million) doses.

4.1.2. Use of normalized event ratios for signal detection

We adopted the approach published (23) by scientists from FDA and CDC to normalize the number of events reported in VAERS for the number of people receiving a particular vaccine or doses administered. This figure can be divided by a similar ratio from a reference vaccine to obtain a normalized event ratio (NER).

We were particularly interested in the H1N1 data, as the paper published by CDC scientists (23) had stated that there had been active efforts to encourage people to use the VAERS system for H1N1 (see p7251 *"These findings, however, should be interpreted in light of the publicity around the 2009-H1N1 vaccine and efforts to increase reporting to VAERS"*).

Examining the data in VAERS (7/30/21) obtained using the WONDER portal, the per population- or per dose- normalized event ratios are very high, particularly for reports of death (177, 98 respectively) (Table 1).

Estimates of PPR are clearly highly muted, challenging their value and appropriateness. Nonetheless, the signal (5.2) for deaths was significant according to the Evans criteria.(24) To the extent that there was any sort of stimulated reporting, this was against a background of extensive campaigns promoting the safety of the C19 vaccines.

Table 1: Normalized Event Ratio (NER) or Proportional Reporting Ratio (PRR) for Covid-19 Vaccines Compared with Seasonal Flue or H1N1 Vaccines

	NER or PPR				
	C19 vs Flu			C19 vs H1N1	
Event Category	NER people[a]	NER Doses[b]	PRR[c]	NER People[d]	PRR[e]
Death	176.7	97.5	5.2*	35.1	0.4
Life Threatening	58.9	32.5	1.7	13.2	1.1
Permanent Disability	29.6	16.3	0.9	19.5	0.7
Congenital Anomaly / Birth Defect *	47.0	26.0	1.4	0.0	0.0
Hospitalized	53.8	29.7	1.6	13.5	1.1
Existing Hospitalization Prolonged	44.3	24.5	1.3	1.3	11.3
Emergency Room * (note)	42.1	32.3	1.7	18.2	0.8
Office Visit * (note)	22.4	17.2	0.9	13.1	1.1
None of the above	37.8	20.9	1.1	15.7	0.9
Serious	51.4	28.3	1.5	14.8	0.97
Not serious	33.1	18.3	1.0	14.9	0.96

We used estimates from CDC for the number of doses delivered/ people vaccinated.[14] We used USAFACTS[15] for age-related population figures for various years, and CDC figures on numbers of people vaccinated [16]for seasonal flu or H1N1 vaccines. Original figures obtained from VAERS 7/30/21 using "USA Territories, unknown"" as the location filter.

[a] Normalized Event Ratio (NER) of number of events in each event category (denominator number of unique events) adjusted for number of people given at least one dose of C19 (all dates) or Flu vaccine for 2016/7, 17/18 or 18/19 seasons

[b] NER of number of events in each event category adjusted for number of doses given of C19 (all dates) or Flu vaccine for 2016/7, 17/18 or 18/19 seasons

[c] PRR, C19, vs. flu (using unique events as denominator)

[d] Ratio of number of events in each event category adjusted for number of people given at least one dose of C19 (all dates) or H1N1 vaccine for 2009/10 season

[14] cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html
[15] usafacts.org/data/topics/people-society/population-and-demographics/population-data/population/
[16] cdc.gov/flu/prevent/vaccine-supply-historical.htm

e PRR C19 vaccines vs. H1N1.

* p <0.00001. (chi squared test). Although other values for example for life-threatening or serious conditions do meet the Evans(24) criteria because they do not exceed 2, the chi-squared test nonetheless yields p<0.00001.

We refined our analysis (Table 2) using VAERS data as of August 6 2021. We considered only reports from the 50 States plus Washington DC, excluding US territories and "unknown" locations to ensure that only AE's reported from the US were used when calculating rates based on vaccination coverage in the US. For the flu vaccines, data from the 2015/16, 2016/17, 2017/18, 2018/19 and 2019/20 were considered. The 2020/21 season was excluded to avoid confounding effects with Covid-19. For the Covid-19 vaccines, reports with an indication of SARS-CoV-2 infection or COVID-19 were not included in counts for COVID-19 vaccines. Because data availability in VAERS is ephemeral, we needed to repeat parts of our earlier analysis on what was the currently available dataset. In addition to deaths and serious events, we examined three categories of events noted to be of interest in the VAERS' Standard Operating Procedures for COVID-19:(21) Guillan-Barré Syndrome (GBS), coagulopathy, and acute myocardial infarction.

Table 2 shows strong signals for serious events, death, coagulopathy and myocardial infarction. The signals are more evident using the Normalized Event Ratio (by dose) than with the PRR. No major differences were evident if the PRR was calculated by number of unique events or by number of unique reports (i.e. symptoms). The values for Normalized Event Ratios (by dose) for death and serious events were similar to those from our earlier analysis (Table 1).

For death and coagulopathy, the signals appear to increase with age. The reverse is true for myocardial infarction. For serious events an age-dependency is not evident. For Guillan-Barré syndrome, the signals appear weak and not detected at all using the DSA/ PRR method.

We conclude from this portion of our work that:

- There are strong safety signals evident for death, serious events, coagulopathy and myocardial infarction associated with the Covid-19 vaccines compared with the flu vaccines.
- Signals are age dependent for death and coagulopathy (increase with age) and myocardial infarction (decreases with age).
- Even after accounting for possible stimulated reporting, by comparison with H1N1 vaccines, strong safety signals are still evident.
- Using Normalized Event Ratios, consistent with CDC published methodology (23) appears a far more sensitive method of identifying signals than DSA/PRR methods.
- Further investigation is warranted to determine causality.
- Caution is warranted as booster doses are being considered.

Table 2: COVID-19 vs. Flu Vaccines: Normalized Event Ratio vs. Disproportionality Signal Analysis as Proportion of All Reports or events

	SERIOUS EVENTS			DEATHS			GBS			COAGULOPATHY			Myocardial Infarction		
Ages	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report
10-17	34	1.66	1.35	32	1.52	1.24	7	0.34	0.28	74	3.56	2.89	n.e.	n.e.	n.e.
18-49	25	0.87	0.99	64	2.22	2.52	3	0.09	0.1	226	7.78	8.82	403	13.92	15.78
50-64	26	1.23	1.45	85	4.01	4.74	3	0.12	0.14	239	11.19	13.22	121	5.68	6.71
65+	30	2.34	2.76	98	7.77	9.16	3	0.22	0.26	370	31.34	36.97	88	7.01	8.27
10+	28	1.31	1.52	91	4.24	4.93	3	0.13	0.15	276	12.77	14.84	126	5.83	6.78

Note: The PRR is the ratio of the proportion of a particular event or event type out of all reports (or events) for COVID-19 to the proportion of all reports (or events) for the combined 2015-2019 flu seasons. Orange shading indicates a statistically significant difference between the proportion of COVID-19 proportion of COVID-19 and flu reports for that age group and event type (chi squared test. Flu reporting rates represent the total reports to VAERS across the 2015/16-2019/20 flu seasons for each age group. Covid-19 reporting rates include all reports to VAERS for COVID-19 vaccines for each age group as of Aug. 6, 2021. The Normalized Event Ratio shown is calculated according to the number of doses given.

The "coagulopathy" category includes a set of 26 preferred terms (PT) for thromboembolic events (although the category does not include coagulopathy PT). The full list of PT's for GBS, coagulopathy and acute myocardial infarctions can be found in Table 4.6 of the VAERS SOP document.(21)

A signal does not prove that the vaccines were the cause of these events. The intense signal for death awaits a transparent explanation[17] that includes a comprehensive report of the types and numbers of investigations performed, including autopsies. Although CDC has provided guidance for the conduct of autopsies of Covid-19 cases, there is no prospective protocol for the conduct of autopsies to determine whether or not the death is vaccine-related. This would include a detailed description of the types of histopathological methods to distinguish vaccine-induced spike protein from spike protein derived from a Covid-19 infection. Where is this analysis? Where is there a protocol? Similarly, the strong signal of heart attacks in younger than in older people (403 vs. 88, Table 1) must be investigated.

Lastly, it is worth discussing the signal for myocarditis, acknowledged to be an issue as a warning in the COMIRNATY package insert attests:(16)

> *"Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose."*

In
Table **3**, we show PRR signals that meet the Evans(24) criteria that are of a similar magnitude (or smaller, except for GBS) to those shown in Table 2, justifying their further investigation.

Table 3: ***COVID-19 vs. Flu Vaccines: PRR for myopericarditis***

Ages	Myopericarditis
12-17	66.8
18-49	5.6
50-64	7.4
65+	4.0
All	7.9

Flu seasons from 2015/16 – 2019/20 were used. Covid vaccine reports were through Aug 6 2021. Reports for codes that includes Covid of SARS-Cov-2 were excluded.

Rapid Cycle Analysis (RCA) of the VSD system was unable to detect a safety signal for myocarditis[18] until data were age stratified. Although in theory RCA should be able to detect signals in near real-time as medical records are being generated, the method appears even less sensitive than those prescribed for VAERS(21) with limitations described above. A paper was published in JAMA (25) on September 3rd describing the findings from the Rapid Cycle Analysis of the VSD system. It concluded that:

> *"incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination."*

We suggest that publication of this paper without the context of the acknowledged myocarditis signals from VAERS, within the conclusion, is highly misleading.

4.2. Estimate of under-reporting in VAERS using CDC published methods

CDC has acknowledged the many limitations inherent in the VAERS system, including that the system is prone to under-reporting for a variety of reasons. There is additional confusion given specific reporting requirements pursuant to the EUA. The CDC web site states[19] that under an EUA, health providers are required to report certain categories of events following

[17] As far as we can tell, the only statement regarding these deaths appears on CDC's web site (9/2/21) *"**Reports of death after COVID-19 vaccination are rare**. More than 369 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, through August 30, 2021. During this time, VAERS received 7,218 reports of death (0.0020%) among people who received a COVID-19 vaccine. FDA requires healthcare providers to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. **Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem.** A review of available clinical information, including death certificates, autopsy, and medical records, has not established a causal link to COVID-19 vaccines."* (their emphasis)
www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

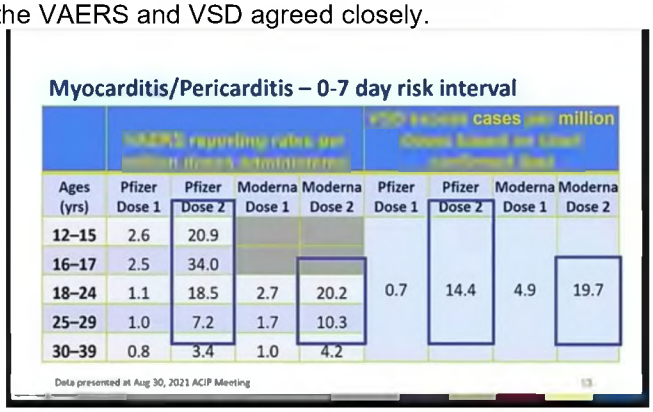
[18] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/04-COVID-Klein-508.pdf

[19] www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/reportingaes.html

vaccination including serious events, deaths and life-threatening events, regardless of if the report think the AE caused the event or not.

With about 2/3 of the US population vaccinated, we would expect about 5000 per deaths to occur every day from non-Covid-19 causes. Using a conservative 30-day follow up, we would expect to see 150,000 deaths reported in VAERS. As of 8/29/21, 6128 deaths (USA, territories and unknown) have been reported in connection with Covid-19 vaccines (4805 deaths 50 States and Washington DC). The system does not appear to be functioning as designed.

In CDC's recent ACIP meeting a number of the presentations referenced data from VAERS without expressing concern that there had been any sort of over- or stimulated reporting. Indeed, the point was made in one presentation,[20] that for myocarditis/ pericarditis at least, the VAERS and VSD agreed closely.



One of the discussants (Dr. Su?) opined that VAERS had captured a substantial portion of these types of reports.

CDC scientists published (26) a method to estimate the degree of under-reporting in VAERS, by comparing the rates of AEs published in clinical trials, with rates normalized for population found in VAERS.

We used the 3 deaths classified as adverse events in Table S3 of the 6 month follow up study for the Pfizer vaccine (27). Conservatively, we did not use the 15 deaths in Table S4 there. Note the discrepancy between total deaths in the Thomas paper (18 vs 19 deaths in vaccine vs. placebo) and in the Summary Basis for Regulatory Action(17) where the total number of deaths reported are 21 and 17 for the vaccine and placebo groups respectively

Using these conservative data, we estimated the numbers of deaths tentatively associated with the Pfizer vaccine may be 4.9-15 times higher than reported. Applied to all vaccines, using the figure of 4805 deaths (50 states. DC) but subtracting deaths where Covid-19 or SARS is mentioned (639) this may represent a true report rate of between 20,400-62,500 deaths. The number of life-threatening events may be 24-64 times higher than reported. Noe that this estimate does not infer causality.

4.3. Estimate of number of deaths possibly associated with Covid-19 vaccines

We have so far estimated 20,400-62,500 deaths unrelated to Covid-19, that we might have expected to find in VAERS (50 States+DC). These non-Covid-related deaths may be related to the toxicity of the spike protein towards heart cells and effects on coagulation. We now estimate deaths related to Covid-19 subsequent to vaccination.

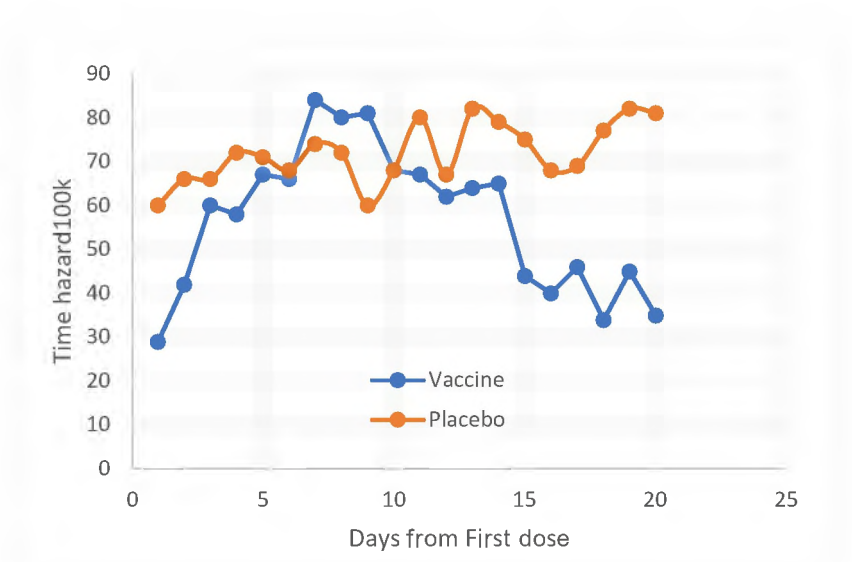
4.3.1. Post-vaccination deaths estimated from Israeli Ministry of Health and Clalit data.

Increased numbers of Covid-19 related deaths associated with vaccination

In an analysis of the data from the initial use (first 44 days) in 596,000 subjects of the Pfizer vaccine in Israel reported by Dagan et al. in NEJM (28), one of us (HS) observed an early (<7 days) uptick in Covid-19 cases following vaccination.

Figure 1: Covid-19 cases following vaccination in Dagan et al.

[20] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/05-COVID-Lee-508.pdf



A letter to NEJM (March 11) was rejected but described in an article in France Soir – May 5.[21] There, the incidences of Covid-19 tripled from day 1 to 7 among the vaccinated,[22] and decreased to their initial rate 20 days after 1st injection, remaining at that level until day 28.The letter continues: "*This suggests a weakened immunity of the vaccinees which causes other, unreported, short-term (non-COVID-19) adverse effects, including some deaths. This analysis should have influenced decisions about who to vaccinate and when. Long-term risks can be expected with age and sex factors.*"

Combining data in Dagan et al., with statistics from the Israeli Ministry of Health, an increase in the number of deaths in vaccinated subjects could be found following vaccination. These Israeli data are particularly informative because by the cut-off date, 54% of adult Israelis had been vaccinated, mitigating to some degree biases due to early vaccination of those most at risk. Further, by combining these data sources, we can see what is happening **among vaccinated patients**. There are a number of limitations as to causality and potential time biases, but this analysis suggests that there may be 121-413 excess deaths/million associated with vaccination, in those vaccinated (>= 1 dose), equating to about 25,000-85,000 deaths in the USA. Again, we cannot ascribe cause, merely association. The recent finding from a large Israeli cohort of an increased (40%) risk of Herpes zoster infection(29) may indicate immunosuppression related to vaccination in some subjects. In one study naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected.(3)

4.3.2. Deaths in the unvaccinated population resulting from transmission by the vaccinated

There is a third pool of deaths and Covid-19 cases that must be considered in assessing the risk and benefits of the Covid-19 vaccines. Contrary to initial hopes, vaccines may not reduce transmission.(30), thus Covid-19 may have been unwittingly transmitted by vaccinees to the non-vaccinated.(31,32) including by fecal aerosol(33) in subjects sharing bathrooms.

4.4. Unresolved pregnancy and reproductive-related related safety issues

4.4.1. Pregnancy

The COMIRNATY package insert(16) provides little guidance for pregnant mothers:

> *"Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy."*

Instead, the prescribing info says: *"There is a pregnancy exposure registry for COMIRNATY. Encourage individuals exposed to COMIRNATY around the time of conception or during pregnancy to register by visiting https://mothertobaby.org/ongoingstudy/covid19-vaccines/."*

[21] francesoir.fr/societe-sante/le-new-england-journal-medecine-refuse-une-lettre-davertissement-du-dr-seligman-sur
[22] The imbalance between the two groups on initiation poses a separate problem as to the matching of the two groups.

As stated in their approval letter,(11) what FDA have done to determine what sorts of risks are posed during pregnancy is to obtain the commitment from BioNTech to conduct a post-marketing pregnancy/neonatal study with a four-year term.

> *Study C4591022, entitled "Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry."*

Note the word commitment. As FDA explains[23]

> "Postmarketing *commitments* (PMCs) are studies or clinical trials that a sponsor has agreed to conduct, but that are *not required* by a statute or regulation."

This is not a requirement (as for some of the other post marketing studies on myocarditis for example). Compare not only this level of regulation, but also the length and scope of the study in question with an unrelated Janssen (J&J) biologic product for which a 7-year[24] study is required and which includes examining effects on child and early development. A recently approved (2021) Astra-Zeneca biologic product[25] requires a NINE-year study on pregnancy and maternal and fetal/neonatal outcomes.

What is disturbing about this situation is that it is in stark contrast to the language in a CDC study protocol entitled: "COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants"[26] and dated June 29 2021:

"Now that COVID-19 vaccines are in use in the U.S., and pregnancy is not a contraindication, there is an urgent need to monitor the safety of these vaccines when administered during or around the time of pregnancy."

The protocol, nonetheless states that the American College of Obstetrics and Gynecology "broadly supports that COVID-19 vaccines be available for use in pregnant women and that pregnant women not be denied vaccination."

Similar language appears in a related CDC protocol entitled "COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety" [27] and dated April 28 2021:

"Nevertheless, there is an urgent need for data to inform pregnant women and their providers deciding whether to receive a COVID-19 vaccine during pregnancy or following an inadvertent exposure."

Are pregnant women being advised about this sort of language and that they are in effect unknowingly participating in a clinical study?

Preliminary findings of a CDC study(34) published in June involving 35,691 pregnant v-safe surveillance system participants and 3958 participants of enrolled in the v-safe pregnancy registry (only 827 of whom had a completed pregnancy), *"did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines."* The study acknowledged that *"more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes."*. This study was updated(35) and declared a cumulative early pregnancy loss rate of 14%. This rate is significantly higher than the published rate for equivalent gestation (more than 6 weeks with dating confirmation of pregnancy) seen(36) of 9% and more recently of 5%.(37) In the same study over 80% of participants were not surveyed and the fetal loss rate of 14% was reported to be potentially higher due to missing data, perhaps reaching 18%. No data has been provided for pregnancies beyond 20 weeks in the later publication and requests for data sharing have been declined by the CDC despite being a publicly funded registry comprising voluntary unpaid participants.

It is also noteworthy that the only study of efficacy of the mRNA vaccine in pregnant women was recently published (38)and failed to show any significant differences in overall hospitalization rates (marginal), severe disease or death in a comparison

[23] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments
[24] www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761061Orig1s000ltr.pdf
[25] www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761123Orig1s000ltr.pdf
[26] www.cdc.gov/vaccinesafety/pdf/COVID19-acute-maternal-outcomes-508.pdf
[27] www.cdc.gov/vaccinesafety/pdf/VSD-COVID-Vaccine-SAB-SB-Protocol-508.pdf

between vaccinated and unvaccinated pregnant women. In the same study no deaths were noted in about 20,000 participants equally distributed between groups. At a published rate of covid death in the pregnant age population of 1 per 100,00028 in fact would require a study of 1.6m people to detect a 50% reduction in mortality. This has not been shown and therefore no claims as to the efficacy of an original strain -specific mRNA vaccine specific against delta SARS-Cov-2 in pregnancy can be reliably made. Given the potential for the unknown teratogenicity involved in this novel therapy it is not possible to make any accurate claims of a positive risk-benefit profile in pregnancy despite overwhelming claims of such by the international OBGYN community.

As with two other related studies (28,29), this study permitted matched control subjects to become vaccinated. A data re-analysis(39) of one of these studies(28) found that that the entire apparent reduction in Covid-19 deaths, attributed to a two-dose vaccine, might instead be entirely due to selection bias occurring due to data censoring when either one of matched pair of subjects was removed from the analysis due to death, or, in the case of control subjects, become vaccinated. A similar bias is likely to operate in this pregnancy study.

4.4.2. Menstrual disorders

On the very same day (August 30) CDC staff were providing evidence to ACIP on the safety of the Pfizer vaccine, NIH made the startling announcement[29] that it was funding studies *"to explore potential links between COVID-19 vaccination and menstrual changes*." They elaborated: *"Some women have reported experiencing irregular or missing menstrual periods, bleeding that is heavier than usual, and other menstrual changes after receiving COVID-19 vaccines."*

Querying VAERS (9/3/21) for various menstrual disorders[30] we found that for reports associated with the Covid-19 vaccines there were 7037 separate menstrual disorder related symptoms described in 4783 unique reports. By comparison with all other vaccines, for ALL years COMBINED we found 897 symptoms in 798 unique events. Most of these are accounted for by the HPV vaccines (698 symptoms in 623 events) with seasonal flu vaccines contributing only 47 symptoms within 45 unique events. Another analysis of VAERS reports also detected menstrual disorders.(40) A similar pattern of symptoms relating to menstrual irregularity was seen in the MHRA yellow card reporting scheme in the UK suggesting that this is not just unique to VAERS reporting.[31]

One explanation for these irregularities is the biodistribution of the LNP based formula which has been shown to be preferentially distributed to, and accumulate in, the ovaries in female animal studies. The full biodistribution data for the LNP component of the Pfizer vaccine from animal studies is now in the public domain following freedom of information requests (41). The biodistribution studies show clearly that although the LNP vector is partially cleared from the injection site at 48 hours it accumulates over 100-fold in the ovaries during the same time period (p45).

No suitable fertility studies were subsequently performed prior to approval of the therapy to ascertain whether this could have an impact in humans and the information regarding accumulation of the product was not made public. Only one animal study addressing the fertility question was assessed prior to the issuance of the EUA which was study 20256434 (p55-56). This included only 22 rats and in each treatment group and within which one female in each group was euthanized due to total litter death. No long term studies of the pups was made as all pups were euthanized. An increased pre-implantation loss rate in rats was noted but no further studies performed.

"Menstrual disorders" are far too often trivialized, leaving its victims and their families to suffer. A number of these disorders lead to early hysterectomies which trigger another set of complications that can include adhesions, pain, bowel obstruction, heart disease and dementia. Will these sorts of problems be examined as part of the NIH studies?

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[28] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1016465/Vaccine_surveillance_report_-_week_36.pdf

[29] www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation

[30] 9/3/21 – searched under "USA, Territories and Unknown" using the terms AMENORRHOEA, DYSMENORRHOEA, HEAVY MENSTRUAL BLEEDING, HYPOMENORRHOEA, MENORRHAGIA, MENSTRUATION DELAYED, MENSTRUATION IRREGULAR.

[31] www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

NIH illustrates a number of reasons for these reported menstrual changes, including *"pandemic-related stress."* But stress is not our prime suspect. Effects on the ovaries and uterus are, and we must view these reported menstrual changes in the context of unresolved questions about the safety of the vaccines on the reproductive system in general, and on pregnancy in particular.

4.5. AE events reported elsewhere

In the United Kingdom, the Yellow Card system(42) for the period 4th January 2021 to 7th July 2021 shows 1,470 deaths and 1,059,307 adverse events (317,025 individual reports) associated with Covid-19 vaccines. European data are available through the EudraVigilance System,[32] from which we estimate the number of deaths associated with the Pfizer, Moderna, J&J and Astra-Zeneca vaccines, combined to be between approximately 3537 and 18926 (2021, to 7/17/21).[33] The WHO provides the Vigiaccess[34] database from which 8,703 deaths and 1,537,994 ADR records were registered as at 26th July 2021.[35]

4.6. Establishment of LTFU program: pCoVS

The growing list of short-term effects attributed to the Covid-19 vaccines, as well as unresolved long term concerns poses a major public health issue. To concretize recognition of, and to spur action to avert and confront this potential public health crisis, we propose the term:

Post Covid Vaccine Syndrome – pCoVS

A syndrome occurring after injection of antigen-inducing, gene therapy vaccines to SARS-Cov-2 virus. The syndrome is currently understood to manifest variously as cardiac, vascular, hematological, musculoskeletal, intestinal, respiratory or neurologic symptoms of unknown long-term significance, in addition to effects on gestation. Manifestations of the syndrome may be mediated by the spike protein antigen induced by the delivered nucleic acids, the nucleic acids themselves, or vaccine adjuvants. As more data become available, subsets and longer-term consequences of pCoVS may become apparent, requiring revision of this definition. Sub-categories may be designated by suffix for example:

-C Cardiac
-N Neurologoc
-H Hematologic
-V Vascular

We propose:

- Recognition by public health agencies, governments and professional societies of pCoVS.
- Assignment of ICD10 and related tracking or re-imbursement codes for pCoVS.
- Establishment of transparent systems to monitor and track for long-term and delayed pCoVS.
- Establishment of funding for research into the prevention and treatment of pCoVS.
- Regulation of the Pfizer, Moderna and Janssen vaccines (GTVs) as Gene Therapy products.
- Insistence on long term (15 years) pharmacovigilance by manufacturers of AI-GTVs for pCoVS consistent with FDA guidelines for gene therapy products.
- Legislation to prevent discrimination of patients based on vaccination[36] or actual or potential pCoVS status.
- Establishment of funding to determine what effects if any the GTVs have on the genome or gene expression, including their effects on toxicity and other disorders. Develop and implement methods to screen for, and treat the consequences of, such genetic changes.

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[32] www.adrreports.eu/en/search_subst.html

[33] The estimate is provided here in the form of a range due to the disclaimer on the database web site "*This website does not provide the total number of cases reported with a fatal outcome."* Because the same fatality may be counted for different reaction types, the number of fatalities appearing in the database may exceed the number of individual patient deaths. The database includes reports from outside of the European Union.

[34] http://vigiaccess.org/

[35] Dr. Tess Lawrie https://ebmcsquared.s3.eu-west-2.amazonaws.com/Yellow+Card+Report_June+21.mp4. See video at 46 minutes. (update, personal communication)

[36] According to one writer, those choosing to remain unvaccinated, rather than being demonized, should be thanked for serving as a valuable control population enabling the effects of vaccines to be more fully evaluated.

- Comprehensive funding for the development of programs to prevent Covid-19 or reduce its impact by promoting good health practices, proper use of nutritional supplements and conduct of well-executed clinical trials to examine the effects of promising repurposed rugs.

5. Efficacy and Risk-Benefit

Although a number of studies are beginning to emerge regarding vaccine efficacy, the major decisions regarding FDA approval and CDC recommendation for the Pfizer vaccine have been based on two studies:

- Pfizer's own study (~40,000) presented at CDC[37] and recently preprinted.(27), with a data cut-off of March 2021.
- The large Israeli Clalit efficacy (~1.2 million) (28) and related safety (~1.7 million) studies.(29)

There are significant sources of bias in the two Israeli studies. Both studies exclude certain high-risk categories of subjects. A data re-analysis of the efficacy study (39) found that that the entire apparent reduction in Covid-19 deaths, attributed to a two-dose vaccine, might instead be entirely due to selection bias occurring due to data censoring when either one of a matched pair of subjects was removed from the analysis due to death, or, in the case of control subjects, become vaccinated. Although the original authors recognized this issue and showed in a sensitivity analysis a reduction in crude efficacy from about 72% to 49%, accounting for censoring that could have occurred over the entire study period could have attenuated the efficacy estimates significantly. Other biases were detected. Due to similar kinds of matching employed in the related safety study (29), a similar censoring bias appears to exist.

6. Repurposed Drugs

Once vaccine effectiveness falls from the 90-95% range towards and below 50% any risk-benefit analysis would change greatly, placing these vaccines in close competition with repurposed drugs with far fewer safety concerns, and effectiveness under different scenarios of 30-60% [hydroxychloroquine;(43-45) ivermectin;(46,47) fluvoxamine;(48) Zinc/Vitamin D/other Vitamins(49,50)]. Options are running out as we consider authorizing a booster dose. At the same time Pfizer have announced that the first patient in their phase 2/3 study received a dose of their proprietary PF-07321332 – a drug intended to treat *"non-hospitalized, symptomatic adult participants who have a confirmed diagnosis of SARSCoV-2 infection and are not at increased risk of progressing to severe illness, which may lead to hospitalization or death."(51)* Will we need to wait another year for the arrival of PF-07321332 when a critical evaluation of the data for HCQ and IVM, as we have done, has revealed significant flaws in key studies(45,46) that have shaped policy on these drugs. Not only have we detected key flaws, but once corrected, impressive efficacy estimates are obtained justifying further study.

Table 4 makes interesting reading.

Table 4: Comparison of Deaths and ADR Reports made in Vigiaccess.org database to 9/13/21 (courtesy Dr. Tess Lawrie)

	Deaths	ADR Reports
ivermectin	20	5650
covid-19 vaccine	10541	1995744
remdesivir	557	7262

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The unintended consequences of COVID-19 vaccine policy: why mandates, passports and restrictions may cause more harm than good

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ABSTRACT

Vaccination policies have shifted dramatically during COVID-19 with the rapid emergence of population-wide vaccine mandates, domestic vaccine passports and differential restrictions based on vaccination status. While these policies have prompted ethical, scientific, practical, legal and political debate, there has been limited evaluation of their potential unintended consequences. Here, we outline a comprehensive set of hypotheses for why these policies may ultimately be counterproductive and harmful. Our framework considers four domains: (1) behavioural psychology, (2) politics and law, (3) socioeconomics, and (4) the integrity of science and public health. While current vaccines appear to have had a significant impact on decreasing COVID-19-related morbidity and mortality burdens, we argue that current mandatory vaccine policies are scientifically questionable and are likely to cause more societal harm than good. Restricting people's access to work, education, public transport and social life based on COVID-19 vaccination status impinges on human rights, promotes stigma and social polarisation, and adversely affects health and well-being. Current policies may lead to a widening of health and economic inequalities, detrimental long-term impacts on trust in government and scientific institutions, and reduce the uptake of future public health measures, including COVID-19 vaccines as well as routine immunisations. Mandating vaccination is one of the most powerful interventions in public health and should be used sparingly and carefully to uphold ethical norms and trust in institutions. We argue that current COVID-19 vaccine policies should be re-evaluated in light of the negative consequences that we outline. Leveraging empowering strategies based on trust and public consultation, and improving healthcare services and infrastructure, represent a more sustainable approach to optimising COVID-19 vaccination programmes and, more broadly, the health and well-being of the public.

SUMMARY BOX

- ⇒ Mandatory COVID-19 vaccine policies have been used around the world during the COVID-19 pandemic to increase vaccination rates. But these policies have provoked considerable social and political resistance, suggesting that they have unintended harmful consequences and may not be ethical, scientifically justified, and effective.
- ⇒ We outline a comprehensive set of hypotheses for why current COVID-19 vaccine policies may prove to be both counterproductive and damaging to public health. Our framework synthesizes insights from behavioural psychology (reactance, cognitive dissonance, stigma, and distrust), politics and law (effects on civil liberties, polarization, and global governance), socio-economics (effects on inequality, health system capacity and social wellbeing) and the integrity of science and public health (the erosion of public health ethics and regulatory oversight).
- ⇒ Our analysis strongly suggests that mandatory COVID-19 vaccine policies have had damaging effects on public trust, vaccine confidence, political polarization, human rights, inequities and social wellbeing. We question the effectiveness and consequences of coercive vaccination policy in pandemic response and urge the public health community and policymakers to return to non-discriminatory, trust-based public health approaches.

INTRODUCTION

Since 2021, mandatory proof-of-vaccination policies have been implemented and justified by governments and the scientific community to control COVID-19. These policies, initiated across the political spectrum, including in most liberal democracies, have spread globally and have involved: workplace mandates (eg, a 'no jab, no job' US federal mandate); green passes/vaccine passports that limit access to social activities and travel (eg, Israel, Australia, Canada, New Zealand and most European countries); school-based mandates (eg, most North American universities); differential lockdowns for the unvaccinated (eg, Austria and Australia); the use of vaccine

Table 1 The global turn towards mandatory COVID-19 proof-of-vaccination policies*

Policy/intervention	Countries
'No jab, no job' mandates (eg, government employees, key workers, public and private sector)	Australia, Canada, China, Costa Rica, Croatia, Czech Republic, Denmark, Egypt, Fiji, France, Ghana, Hungary, Italy, Kazakhstan, Latvia, Lebanon, New Zealand, Oman, Poland, Philippines, Russia, Saudi Arabia, Tunisia, Turkey, Ukraine, USA
Healthcare worker mandates	Australia, Britain, Canada, Croatia, Czech Republic, England, Finland, France, Germany, Greece, Hungary, Lebanon, New Zealand, Poland, USA (some states)
Internal vaccine passports to attend social events, restaurants, bars, nightclubs, fitness facilities, entertainment venues and for bus/train/airport travel	Australia, Austria, Britain, Bulgaria, Canada, Czech Republic, Denmark, Egypt, France, Germany, Italy, Israel, Kenya, Lebanon, Morocco, Netherlands, Romania, Serbia, Singapore, Switzerland, South Korea, Ukraine, USA (some states)
School-based mandates	Canada (several provinces), Costa Rica, Lithuania and USA (some states)
Full country mandatory vaccination	Austria, Ecuador, Germany, Indonesia, Micronesia, Turkmenistan, Tajikistan
Full population mandate for the elderly	Czech Republic, Greece, Malaysia, Russia

*This is not a comprehensive list of policies, which are rapidly changing in early 2022. This list excludes the use of segregated lockdowns of the unvaccinated (eg, Austria, Germany, Australia), entry requirements for international travel, fines and penalties (including restricted access to social services and medical care, business capacity restrictions and threats of imprisonment) and the use of vaccine metrics to inform other restrictions. There is a significant variation in how countries recognise infection-derived immunity, allow religious, philosophical and/or medical exemptions and incorporate testing as an alternative to vaccination. In addition, some countries have implemented a combination of policies and interventions, so each is not mutually exclusive. As of March 2022, some countries also shifted course and decided to not implement these policies due to changing epidemiological circumstances and sociopolitical resistance. Adapted from Reuters.[136]

metrics in lifting lockdowns and other restrictions (eg, Australia, Canada and New Zealand); differential access to medical insurance and healthcare (eg, Singapore); and mandatory population-wide vaccination with taxes, fines, and imprisonment for the unvaccinated (eg, the Philippines, Austria, Greece) (see table 1).

The publicly communicated rationale for implementing such policies has shifted over time. Early messaging around COVID-19 vaccination as a public health response measure focused on protecting the most vulnerable. This quickly shifted to vaccination thresholds to reach herd immunity and 'end the pandemic' and 'get back to normal' once sufficient vaccine supply was available.[1 2] In late summer of 2021, this pivoted again to a universal vaccination recommendation to reduce hospital/intensive care unit (ICU) burden in Europe and North America, to address the 'pandemic of the unvaccinated'.

COVID-19 vaccines have represented a critical intervention during the pandemic given consistent data of vaccine effectiveness averting COVID-19-related morbidity and mortality.[3–6] However, the scientific rationale for blanket mandatory vaccine policies has been increasingly challenged due to waning sterilising immunity and emerging variants of concern.[7] A growing body of evidence shows significant waning effectiveness against infection (and transmission) at 12–16 weeks, with both Delta and Omicron variants,[8–13] including with third-dose shots.[14 15] Since early reports of post-vaccination transmission in mid-2021, it has become clear that vaccinated and unvaccinated individuals, once infected, transmit to others at similar rates.[16] Vaccine effectiveness may also be lower in younger age groups.[17] While higher rates of hospitalisation and COVID-19-associated morbidity and mortality can indeed be observed among the unvaccinated across all age groups,[3–6] broad-stroke passport and mandate policies do not seem to recognise the extreme risk differential across populations (benefits are greatest in older adults), are often justified on the basis of reducing transmission and, in many countries, ignore the protective role of prior infection.[18 19]

Mandate and passport policies have provoked community and political resistance including energetic mass street protests.[20 21] Much of the media and civil debates in liberal democracies have framed this as a consequence of 'anti-science' and 'right-wing' forces, repeating simplistic narratives about complex public perceptions and responses. While vaccine mandates for other diseases exist in some settings (eg, schools, travel (eg, yellow fever) and, in some instances, for healthcare workers (HCWs)),[22] population-wide adult mandates, passports, and segregated restrictions are unprecedented and have never before been implemented on this scale. These vaccine policies have largely been framed as offering 'benefits' (freedoms) for those with a full COVID-19 vaccination series,[23 24] but a sizeable proportion of people view conditioning access to health, work, travel and social activities on COVID-19 vaccination status as inherently punitive, discriminatory and coercive.[20 21 25–28] There are also worrying signs that current vaccine policies, rather than being science-based, are being driven by sociopolitical attitudes that reinforce segregation, stigmatisation

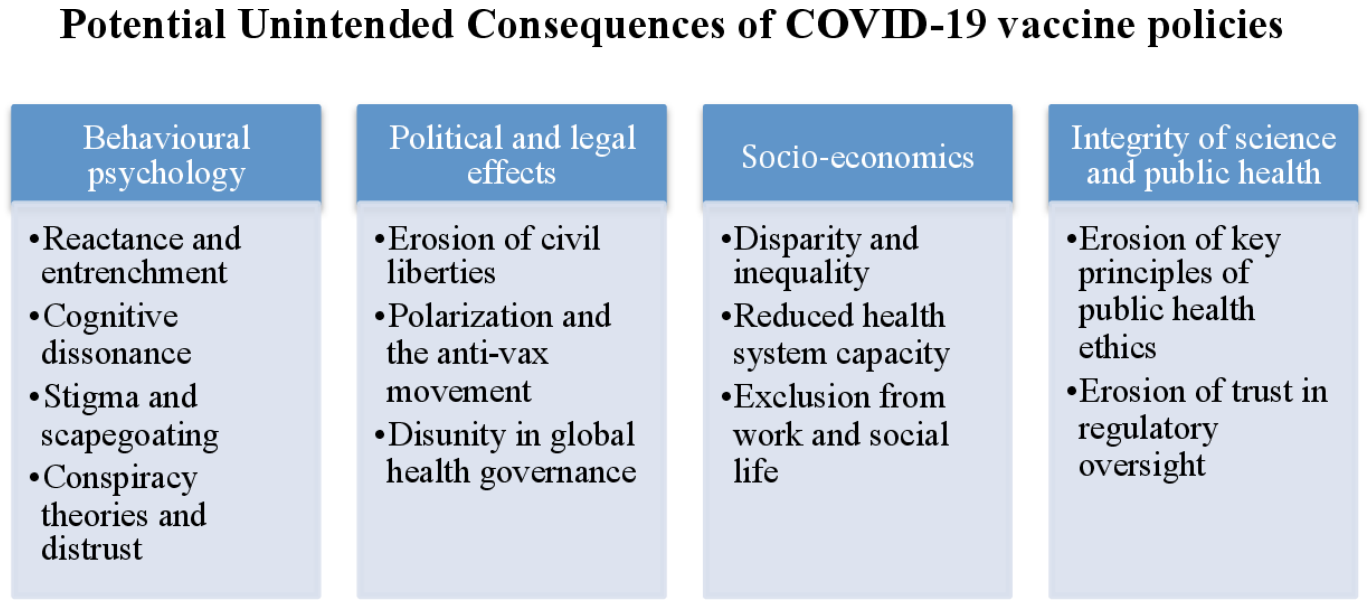

Figure 1 Conceptual framework. We consider a broad conceptual framework spanning core aspects of behavioral psychology, politics and the law, the socio-demographic drivers of health inequality and the integrity of science and public health.

and polarisation, further eroding the social contract in many countries. Evaluating the potential societal harms of COVID-19 pandemic restrictions is essential to ensuring that public health and pandemic policy is effective, proportionate, equitable and legally justified.[29 30] The complexity of public responses to these new vaccine policies, implemented within the unique sociopolitical context of the pandemic, demands assessment.

In this paper, we reflect on current COVID-19 vaccine policies and outline a comprehensive set of hypotheses for why they may have far-reaching unintended consequences that prove to be both counterproductive and damaging to public health, especially within some sociodemographic groups. Our framework considers four domains: (1) behavioural psychology, (2) politics and law, (3) socioeconomics, and (4) the integrity of science and public health (see figure 1). Our aim is not to provide a comprehensive overview or to fully recapitulate the broad ethical and legal arguments against (or for) COVID-19 vaccine mandates and passports. These have been comprehensively discussed by others.[31–33] A full review of the contribution of mandates and passports to COVID-19 morbidity and mortality reductions is not yet possible, although some existing studies on vaccine uptake are cited below. Rather, our aim is to add to these existing arguments by outlining an interdisciplinary social science framework for how researchers, policymakers, civil society groups and public health authorities can approach the issue of unintended social harm from these policies, including on public trust, vaccine confidence, political polarisation, human rights, inequities and social well-being. We believe this perspective is urgently needed to inform current and future pandemic policies. Mandatory population-wide vaccine policies have become a normative part of pandemic governance and biosecurity response in many countries. We question whether this has come at the expense of local community and risk group adaptations based on deliberative democratic engagement and non-discriminatory, trust-based public health approaches.

WHAT CAN WE LEARN FROM THE BEHAVIOURAL SCIENCES?

Reactance, entrenchment and vaccine uptake

Apart from mandatory vaccination of the elderly (planned in Czech Republic, Greece, Malaysia and Russia), most policies do not specify individuals at higher risk of severe COVID-19 outcomes–among whom COVID-19 vaccine uptake rates, and vaccine confidence, are very high.[34 35]

Although studies suggest that current policies are likely to increase population-level vaccination rates to some degree,[36–39] gains were largest in those under 30 years old (a very low-risk group) and in countries with below average uptake.[36] Moreover, insights from behavioural psychology suggest that these policies are likely to entrench distrust and provoke *reactance*—a motivation to counter an unreasonable threat to one's freedom. Literature reviewed by Drury *et al*,[40] including a survey by Porat *et al*[41] in the UK and Israel, found that compulsory COVID-19 vaccination would likely increase levels of anger, especially in those who are already mistrustful of authorities, and do little to persuade the already reluctant. Two experiments in Germany and the USA found that a new COVID-19 vaccine mandate would likely energise anti-vaccination activism, reduce compliance with other public health measures, and decrease acceptance to future voluntary influenza or varicella (chickenpox) vaccines.[42 43] A third experiment found that selective mandates increased reactance when herd immunity targets were not clearly explained[44]—which

most governments failed to communicate adequately and convincingly as they shifted their rationale from herd immunity to hospital/ICU admission metrics. De Figueiredo *et al*[45] found that vaccine passports in the UK would induce a net *decrease* in inclination to get vaccinated among those who had not received a full vaccination dose, while Bell *et al*[46] found that UK HCWs who felt pressured to get vaccinated were more likely to have declined the COVID-19 vaccine. Jørgensen *et al*[47] found that the reintroduction of vaccine passports in late 2021 in Denmark increased distrust among the unvaccinated. Finally, recent evidence from France suggests that the *passe sanitaire* was associated with increased vaccination but that it did so to a lower extent among the most vulnerable, may have contributed to increased nocebo effects and did not reduce vaccine hesitancy itself; the authors concluded: "Mandatory vaccination for COVID-19 runs the risk of politicising vaccination further and reinforcing distrust of vaccines."[48]

Cognitive dissonance

The public interpretation of these policies has occurred within the context of the rapidly changing pandemic. Oftentimes, public announcements and media coverage have oversimplified, struggled to communicate potential adverse events (including a potentially higher risk in the convalescent)[49] and overstated vaccine efficacy on transmission. Significant public concerns about safety signals and pharmacovigilance have been furthered by the lack of full transparency in COVID-19 clinical trial data[50 51] as well as shifting data on adverse effects, such as blood-clotting events,[52] myocarditis[53] and altered menstrual periods.[54] These changes have been associated with changes to vaccination guidelines in terms of eligibility for different vaccines in some countries. Mandates, passports and segregated restrictions create an environment where reactance effects are enhanced because people with low vaccine confidence see contradictory information as validating their suspicions and concerns. The pressure to vaccinate and the consequences of refusal heighten people's scrutiny of information and demand for clarity and transparency. Current policies have likely facilitated various layers of *cognitive dissonance*—a psychological stress precipitated by the perception of contradictory information.

Citing the potential for backlash and resistance, in December 2020, the director of the WHO's immunisation department stated: "I don't think we envision any countries creating a mandate for [COVID-19] vaccination."[55] Many governments originally followed with similar public statements, only to shift positions, often suddenly, in mid or late 2021 during the Delta or Omicron surge, including in Austria (the first country to announce a full population-wide mandate).[56 57] Cognitive dissonance may have been compounded by the changing rationale provided for vaccine mandate policies, which originally focused on achieving herd immunity to stop viral transmission and included public messaging that vaccinated people could not get or spread COVID-19. Policies often lacked clear communication, justification and transparency, contributing to persistent ambiguities and public concerns about their rationale and proportionality.[58] In late 2021, however, the re-introduction of onerous non-pharmaceutical interventions in countries with mandates and passports perpetuated cognitive dissonance, since governments had made promises that vaccination would ensure a 'return to normal' and many people (especially younger people) had vaccinated based on these announcements.[36 48]

When mandate rules are perceived to lack a strong scientific basis, the likelihood for public scrutiny and long-term damage to trust in scientific institutions and regulatory bodies is much higher. A good example is the lack of recognition of infection-derived immunity in employer-based vaccine mandates and passports in North America, including most universities and colleges.[59] Despite clear evidence that infection-derived immunity provides significant protection from severe disease on par with vaccination,[18 31] prior infection status has consistently been underplayed. Many individuals with post-infection immunity have been suspended or fired from their jobs (or pushed to leave) or been unable to travel or participate in society[31 56–59] while transmission continued among vaccinated individuals in the workplace. This inconsistency was widely covered in American conservative and libertarian-leaning media in ways that reinforced distrust not only about the scientific basis of vaccine policies but also the entire public health establishment, including the US Centers for Disease Control and Prevention (CDC).

Stigma as a public health strategy

Since 2021, public and political discourse has normalised stigma against people who remain unvaccinated, often woven into the tone and framing of media articles.[60] Political leaders singled out the unvaccinated, blaming them for: the continuation of the pandemic; stress on hospital capacity; the emergence of new variants; driving transmission to vaccinated individuals; and the necessity of ongoing lockdowns, masks, school closures and other restrictive measures (see table 2). Political rhetoric descended into moralising, scapegoating, and blaming using pejorative terms and actively promoting stigma and discrimination as tools to increase vaccination. This became socially acceptable among pro-vaccine groups, the media and the public at large, who viewed full vaccination as a moral obligation and part of the social contract.[61] The effect, however, has been to further polarise society—physically and psychologically—with limited discussion of specific strategies to increase uptake especially in communities where there would be disproportionately larger individual and societal benefits. There is rarely a discussion of *who* and *why* people remain unvaccinated. Vaccine policy appears to have driven social attitudes towards an us/them dynamic rather than adaptive strategies for different communities and risk groups.

Table 2 Political rhetoric regarding the unvaccinated

Country leader	Statement
Emmanuel Macron, PM of France	"[It is] only a very small minority who are resisting. How do we reduce that minority? We reduce it by pissing them off even more…When my freedoms threaten those of others, I become someone irresponsible. Someone irresponsible is not a citizen."[117]
Justin Trudeau, PM of Canada	"When people are seeing cancer treatments and elective surgeries put off because beds are filled with people who chose not to get vaccinated, they're frustrated…When people see that we are in lockdowns or serious public health restrictions right now because of the risk posed to all of us by unvaccinated people, people get angry." "They are extremists who don't believe in science, they're often misogynists, also often racists…It's a small group that muscles in, and we have to make a choice, as a leader and as a country: Do we tolerate these people?"[137]
Joe Biden, President of the USA	"This is a pandemic of the unvaccinated. And it's caused by the fact that despite America having an unprecedented and successful vaccination program, despite the fact that for almost five months free vaccines have been available in 80 000 different locations, we still have nearly 80 million Americans who have failed to get the shot."[138] "For the unvaccinated, you're looking at a winter of severe illness and death for yourselves, your families, and the hospitals you may soon overwhelm."[139]
Naftali Bennett, PM of Israel	"Dear citizens, those who refuse vaccines are endangering their health, those around them and the freedom of every Israeli citizen. They are endangering our freedom to work, the freedom of our children to learn and the freedom to hold celebrations with the family. Those who refuse vaccines hurt us all because if all of us were vaccinated, we would all be able to maintain daily life. But if one million Israelis continue to not get vaccinated, this will oblige the eight million others to shut themselves in their homes."[140]
Michael Gunner, Northern Territories Chief Minister, Australia	"If you are anti-mandate, you are absolutely anti-vax, I don't care what your personal vaccination status is. If you support, champion, give a green light, give comfort to [or] support anybody who argues against the vaccine, you are an anti-vaxxer, absolutely. Your personal vaccination status is not relevant. If you campaign against the mandate…If you say 'pro-persuasion', stuff it, shove it. You are anti-vax."[141]
Jacinda Ardern, PM of New Zealand,	"If you are still unvaccinated, not only will you be more at risk of catching COVID-19, but many of the freedoms others enjoy will be out of reach…. we have managed very high vaccination rates, generally, without the use of certificates but what has become clear to me is that they are not only a tool to drive up vaccines; they are a tool for confidence. People who are vaccinated will want to know that they are around other vaccinated people…it is a tool for business."[142]
Tony Blair, former UK PM	"We need to target the unvaccinated. Frankly if you are unvaccinated at the moment and you're eligible and have no health reason for being unvaccinated, you're not only irresponsible but you're an idiot. I am sorry but truthfully you are. With this Omicron variant…you will get it and this will put a lot of strain on the health service."[143]
Rodrigo Duterte, President of the Philippines	"I'm now giving orders to village leaders to look for those persons who are not vaccinated and request them to stay put [in their house]…If they refuse to vaccinate, or continue to leave their home, the village leaders are empowered to arrest them…."[144]

PM, Prime Minister.

Leveraging stigma as a public health strategy, regardless of whether or not individuals are opposed to vaccines, is likely to be ineffective at promoting vaccine uptake.[62] Unvaccinated or partially vaccinated individuals often have concerns that are based in some form of evidence (eg, prior COVID-19 infection, data on age-based risk, historical/current trust issues with public health and governments, including structural racism), personal experiences (eg, direct or indirect experience of adverse drug reactions or iatrogenic injuries, unrelated trauma, issues with access to care to address adverse events, etc) and concerns about the democratic process (eg, belief that governments have abused their power by invoking a constant state of emergency, eschewing public consultation and over-relying on pharmaceutical company-produced data) that may prevent or delay vaccination.[45 46 63–66] Inflammatory rhetoric runs against the pre-pandemic societal consensus that health behaviours (including those linked to known risk factors for severe COVID-19, for example, smoking and obesity) do not impact the way medical, cultural or legal institutions treat individuals seeking care. Some governments discussed or imposed medical insurance fines or premiums on the unvaccinated, while hospital administrators considered using vaccination status as a triage protocol criterion. The American Medical Association released a statement decrying the refusal to treat unvaccinated patients[67] but this has not prevented the ongoing narrative of shaming and scapegoating people choosing not to get vaccinated.

Trust, power and conspiracy theories

Trust is one of the most important predictors of vaccine acceptance globally[68 69] including confidence in COVID-19 vaccines.[63 70 71] Data show that being transparent about negative vaccine information increases trust and Petersen *et al*[72] found that when health authorities are not transparent, it can increase receptivity to alternate explanations.

COVID-19 vaccine policies have the potential to erode vaccine confidence, trust and the social contract in the particular context of the pandemic, which has exacerbated social anxieties, frustrations, anger and uncertainty. By the time COVID-19 vaccine mandates were introduced, many communities had struggled under lockdowns and other severe public health restrictions, undergone a succession of pandemic waves with changing rules that stretched public confidence in government, had their economic security and livelihoods negatively impacted and been exposed to a media-induced culture of fear perpetuated by an abundance of conflicting and confusing information. All of this occurred within the broader global trend of increasing inequities between North and South, rich and poor, as well as the erosion of trust in institutions and experts.

It is likely that many of the alternative explanations of the pandemic, often called conspiracy theories, were further entrenched when vaccine policies were forcefully implemented in 2021, creating a strong confirmation bias that governments and corporate powers were acting in an authoritarian manner. Those who resist vaccine mandates and passports are more likely to have low trust in government and scientific institutions,[25–28 63 64] and these beliefs and distrust have likely grown due to the propensity of policies to justify social segregation, creating new forms of activism. Furthermore, multiple social perceptions and logics about science, technology and corporate and government power have been grafted onto the public discussion about COVID-19 vaccines, specifically related to authoritarian biosurveillance capabilities.[73] These include concerns about the adoption of implantable tracking devices (including microchips), digital IDs, the rise of social credit systems and the censorship of online information by technology companies and state security agencies. The COVID-19 pandemic happens to coincide with far-reaching technological advances that do provide the capability for new forms of mass state surveillance.[74 75] For example, emerging biocompatible intradermal devices can be used to hold vaccine records,[76] while multifunction implantable microchips (that can regulate building access and financial payments, much like cellphones) are now available on the market.[77] Aspects of vaccine passport policies (dependent on QR codes) combined with these innovations—as well as censorship by social media companies of vaccine clinical trial and safety issues from reputable sources like the BMJ[78]—have likely reinforced and exacerbated suspicion and distrust about the impartiality of public health guidance and vaccines.[79] It is highly likely that reactance effects generated by current vaccine policies have increased the view that public health is influenced by powerful sociopolitical forces acting in the private interest, which may damage future social trust in pandemic response.

THE POLITICAL AND LEGAL EFFECTS OF VACCINE MANDATES, PASSPORTS AND RESTRICTIONS

The erosion of civil liberties

The COVID-19 vaccine policies that we have outlined represent a broad interference with the rights of unvaccinated people. While some governments introduced mandates and passports through the democratic process (eg, Switzerland, Austria, France), many policies were imposed as *regulations*, *decrees*, *orders* or *directions* under states of emergency and implemented in ways that allowed ad hoc juridical decisions and irregular and overpermissive private sector rules, with limited accountability or legal recourse to address rights violations.[58]

Vaccine passports risk enshrining discrimination based on *perceived* health status into law, undermining many rights of healthy individuals: indeed, unvaccinated but previously infected people may generally be at *less* risk of infection (and severe outcomes) than doubly vaccinated but infection-naïve individuals.[80] A weekly negative SARS-CoV-2 test is often seen as a compromise in lieu of full vaccination status, but this places additional burdens (including financial) on the unvaccinated while also risking reputational damage. Employer-imposed mandates that do not provide reasonable accommodation (eg, testing, relocation or reassignment of duties) or that require people to be vaccinated following prior infection even where employees can work remotely, arguably constitute a disproportionate imposition of a health intervention without workplace-related justification.[81] Many countries have also tightened the ability to seek religious, medical or philosophical exemptions, open to unclear decision-making and political interference.[82] Perhaps the most high-profile case to date involves the deportation of the top-ranked men's tennis player, Novak Djokovic, at the Australian Open 2022, despite having been granted a medical exemption on the basis of documented prior infection.[83] While media outlets were quick at hinting about problems in his official submission, the Minister of Immigration accepted that he had a valid test result and that he posed only a 'very low' risk to the health of Australians.[84] Yet, the court ruled that it was reasonable for the Minister to conclude that Mr Djokovic's presence could 'foster anti-vaccination sentiment' and thus have a negative impact on vaccination and boosters.[84] It endorsed Mr Djokovic characterisation as a threat to Australian 'civil order and public health'.[83 84] The case underlines concerns of vaccine mandates and passports as a tool for disproportionate policy that circumvents normative civil liberties and process.

There are also significant privacy issues with passports, which involve sharing medical information with strangers.

Having set these population-wide passport precedents, it is conceivable that they could be expanded in the near future to include other personal health data including genetic tests and mental health records, which would create additional rights violations and discrimination based on biological status for employers, law enforcement, insurance companies, governments and tech companies. COVID-19 vaccine passports have normalised the use of QR codes as a regulated entry requirement into social life; in France and Israel, double-vaccinated citizens lost their 'status' when passports required a booster dose in 2021/2022.[85 86] Technology companies interested in biosurveillance using artificial intelligence and facial recognition technology have obtained large contracts to implement vaccine passports and now have a financial interest in maintaining and expanding them.[87]

Political polarisation

COVID-19 vaccine policies have generated intense political debate, mass street protests and energised new populist movements with varied political views.[20 21 25–28 56] Studies show that while many support these policies, others view them as inherently coercive, discriminatory, disproportionate and counter to liberal values of bodily autonomy, freedom of choice and informed consent.[25–28] It is clear that current policies are divisive and unpopular with many, even vaccinated people, and that they have become a source for collective rage and anger, notably for those who have been fired from their jobs or isolated and barred from social life.

COVID-19 vaccine policies may influence upcoming elections. For instance, right-wing and populist parties in Germany (the Alternative for Germany), Canada (People's Party) and Austria (Freedom Party) have come out strongly against medical segregation. After implementing the world's first population-wide mandatory vaccine policy in February 2022, Austria suspended it 6 days before police would impose fines (max €3600), partially due to legal concerns, mass street protests and the fact that the rate of vaccination had not significantly improved (20% of adults remain unvaccinated).[56 88] In 2022, the US Supreme Court struck down the Biden administration's federal vaccine mandate as unconstitutional,[89] just as it came into effect for 80 million workers (although upholding the mandate for HCWs); republicans had long criticised the mandates.[90 91] In Martinique and Guadalupe, vaccine passports have led to months of political unrest and violent protests that threaten the stability of the French government.[48] Pottinger[92] argued that mandates and passports could trigger insurrection and civil war in South Africa.

Just as the smallpox vaccination mandates in 1850s Britain created the first 'anti-vax' movement,[93] the backlash against COVID-19 policies is energising a global network connected by modern communication technology against these measures. These backlashes may contribute to increased distrust of other vaccines and foster new forms of radicalisation and protest. While mainstream news outlets have voiced concern about the rising 'anti-vaccination fervour' among the far-right, and potential for violence,[94] centre and left politicians have also used this rhetoric for their own agenda. In Canada, Prime Minister Trudeau used majority support for mandatory vaccination and passports to divide the conservative opposition in the 2021 federal election. The end to exemptions for unvaccinated truckers crossing the US–Canadian border precipitated the trucker 'freedom convoy' protests in early 2022 in Canada, which led to weeks of protesters occupying streets outside parliament. The protest ended with the unprecedented invoking of the Emergencies Act, equivalent to martial law, which was heavily criticised by civil liberty organisations and included the freezing of protester bank accounts.[95 96] In the USA, California and New York (Democrat-controlled states) have implemented COVID-19 vaccine passports for children while Florida, Georgia and Texas (Republican-controlled) are introducing legislation to remove childhood school vaccine mandates in general. Some medical freedom and anti-vaccination groups have made increasingly false and inflammatory claims, and business owners and employees requiring QR codes for entry have been targeted for abuse, in some cases. In turn, pro-vaccine advocates have equated anti-mandate social groups as 'anti-vaxxers' and even domestic terrorists, calling for government agencies and social media companies to strengthen censorship laws. Echo chambers have skewed the reasonableness of risk assessment of some pro-mandate individuals, who now fear that unvaccinated people are 'unsafe'—physically but also culturally—despite the scientific evidence. Political polarisation and radicalisation—both anti-mandate and pro-mandate—will increase if punitive vaccine policies continue.

Disunity in global health governance

Current vaccine policies risk furthering disunity in global health governance. Despite the WHO stating in early 2022 that boosters would prolong the pandemic by contributing to vaccine hoarding and low supply,[97] universities (including some global health departments) in wealthy countries have mandated boosters for low-risk healthy students and faculty,[59] when vaccination rates remained low in many low/middle-income countries (LMICs).[98] Efforts to pressure pharmaceutical companies (who developed vaccines with the support of publicly funded research money) to remove patent protections have proven unsuccessful.[99 100] Pharmaceutical companies have ensured that the costs of adverse effects are borne by governments[101] ; in turn, the world's tens of millions of migrants and asylum-seekers may be denied COVID-19 vaccines because of legal liability issues.[102] Simultaneously, some scientists are calling the unvaccinated (as a homogeneous group) the source of future variants ('variant factories') fuelling inflammatory rhetoric[103] that may have contributed to the heavily criticised reaction to close international borders to southern Africa during the spread of Omicron in late 2021. International

travellers, especially from the global south, have been barred from travelling to high-income countries based on the type of received vaccine.

The rollout of vaccine passports and mandates is financially costly and diverts resources and focus away from other interventions. In Canada, $1 billion was pledged by the Trudeau government for vaccine passports[104] and in New York State, the Excelsior Pass App-system developed by IBM will cost more than $27 million.[87] Importantly, focus on 'the unvaccinated' as the cause of health system collapse diverts public attention away from global equity failures and deep structural challenges facing public health capacity in many countries. It absolves governments of attending to other strategies for opening schools and keeping public spaces safe, including improved ventilation and paid sick leave. The indiscriminate global adoption of current COVID-19 vaccine policies may also compromise national sovereignty by skewing health priorities in LMICs, taking budgets away from other important health priorities and disregarding public opinion—a new form of vaccine colonialism. Perhaps more significantly, it is possible that vaccination metrics become tied to international financial agreements and development loans and that pharmaceutical and technology companies influence the global adoption of passport systems and mandate policies for the current but also future pandemics.

SOCIOECONOMIC IMPACTS

Increasing disparity and inequality

Historically, marginalised groups—those facing economic challenges and racial and minority groups—tend to have less confidence in vaccination programmes and are more likely to be distrustful.[63–66 68–71] This raises the possibility that current vaccine policies may fuel existing inequity.[105] A rapid policy briefing by the Nuffield Council on Bioethics[106] emphasised that immunity passports could 'create coercive and stigmatising work environments' and are 'more likely to compound than redress…structural disadvantages and…social stigmatisation'.[106] It is highly likely that mandates and passports have been implemented in ways that discriminate against disadvantaged groups including immigrants, the homeless, isolated elderly people, those with mental illness, specific cultural and religious groups, those in precarious living circumstances, and people with certain political views and values. Moreover, communities who have historically been subject to state surveillance, segregation, structural racism, trauma or violence may be more likely to resist medical mandates. In Israel, reports suggest that Bedouin and Palestinian communities in the Occupied Palestinian Territory have faced major barriers to vaccine access, with more distrust of vaccination and bureaucratic barriers to accessing and using green passes even when vaccinated.[58] Similar challenges have been raised among Europe's Roma and in black communities in the UK and USA.[45 66 107] Altogether, rather than enhancing human agency and strengthening communities and social cohesion, many current vaccine policies—including monthly fines for non-compliance (eg, Greece and Austria)—may work to disempower individuals and contribute to long-term psychosocial stress and disharmony.

Reduced health system capacity

The pandemic has created immense strain on health systems, contributing to disruptions in global immunisation programmes[108] and burnout in healthcare and social care workers that risk worsening clinical outcomes for all patients. These trends may be exaggerated by the current policy push towards mandatory COVID-19 vaccination of healthcare/social care workers and firing of unvaccinated staff. The ethical arguments against these policies have been outlined by others.[31 33 109]

Despite these considerations, many countries may lose frontline staff due to mandates. By December 2021, despite the forthcoming imposition of a (later rescinded) vaccine mandate for patient-facing National Health Service (NHS) workers, 8% of medical practitioners in the UK (73 000 people) remained unvaccinated.[110] In late 2021, Quebec (Canada) dropped its proposed mandate for HCWs, citing the devastating labour shortage it would cause in hospital systems (3% of staff, or 14 000, were unvaccinated).[111] Both cases created immense stress on already overburdened health staff and administrators, and were decried for their lack of clarity and clumpy policy process.[112]

Exclusion from work and social life

COVID-19 vaccination policies that disproportionately restrict people's access to work, education, public transport and social life can be considered a violation of constitutional and human rights.[113] The economic effects of restricting access to work may also have indirect implications for dependents of the unvaccinated. A survey in October 2021 in the USA found that 37% of unvaccinated participants (5% of participants overall) would leave their job if their employer required them to get a vaccine or get tested weekly; this rose to 70% of unvaccinated participants (9% of all participants) if weekly testing was not an option.[114] Economic deprivation and parental stress resulting from restricted access to work and exclusion from social life may have long-term psychological and livelihood consequences on individuals, families and especially children.[30] Commentators have also highlighted the potential impact of mandates in creating supply chain bottlenecks in certain commodities and with cross-border trade and argued that changing vaccine rules and regulations threaten to negatively impact overall economic recovery in some sectors of the economy including tourism.[115]

THE INTEGRITY OF SCIENCE AND PUBLIC HEALTH

Erosion of key principles of public health ethics and law

Current vaccine policies may erode core principles of public health ethics. As some of those supporting

mandates recognise,[113 116] and contrary to the media portrayal that 'the unvaccinated are entirely free to decline', many COVID-19 vaccine policies clearly limit choice and the normal operation of informed consent. This has placed medical professionals in an awkward position, blurring the lines between voluntary and involuntary vaccination. It is clear that many who are vaccinated did so because of the serious consequences of refusal, such as loss of employment and livelihood or access to social events and travel. We should pause to consider the extent to which current policies, and how they are implemented in clinical settings, sets a precedent for the erosion of informed consent into the future and impact the attitude of the medical profession to those who are reticent to undergo a specific medical procedure.

According to public health ethics, the principle of proportionality requires that the benefits of a public health intervention must be expected to *outweigh* the liberty restrictions and associated burdens.[32] It would violate the proportionality principle to impose significant liberty restrictions (and/or harms) in exchange for trivial public health benefits, particularly when other options are available. Evidence shows that the efficacy of current COVID-19 vaccines on reducing transmission is limited and temporary,[7–16] likely lower in younger age groups targeted for vaccine mandates and passports[36] and that prior infection provides, roughly speaking, comparable benefit.[18 31 80] The effectiveness of vaccine mandates in reducing transmission is likely to be smaller than many might have expected or have hoped for, and decrease over time. These issues have been widely discussed in the public arena, raising the idea that many current vaccine policies are no longer being guided by the best science but are rather being used to punish individuals who remain unvaccinated and to shape public opinion and compliance. Some governments have publicly admitted this much; in the words of French President Emmanuel Macron, the aim is to 'piss off [the unvaccinated] …to the end. This is the strategy.'[117] Mandating a third dose for young boys to attend college or university in America has been widely discussed in the US media despite the lack of evidence for substantial clinical benefit,[59 118] and with evidence of small but still significant risk of myocarditis that compounds with each dose.[119–121] Scandinavian countries have taken a precautionary and voluntary approach in their recommendations to the vaccination of children, with Swedish authorities stating that '[because of] a low risk for serious disease for kids, we don't see any clear benefit with vaccinating them'.[122] This furthers the perception that current COVID-19 school vaccine mandates (eg, in California) are disproportionate, especially as safety studies in young children remain relatively sparse.[123]

Proportionality is also a key condition from a constitutional and human rights perspective.[113 124 125] The formal requirements of legal proportionality tests, which differ slightly depending on jurisdiction and context, generally reflect a balancing similar to the one in public health ethics. In part because of legally required restraint when it comes to assessing the reasonableness of complex policy interventions, several courts, human rights tribunals and committees, and labour arbitrators have upheld mandates as proportionate or made statements as to their legitimacy.[113] This appears to have led to a broad presumption that mandates are legally unproblematic. But a common requirement of legal proportionality is that no other, less rights-restricting measures are available that can reasonably achieve the key public health goal. Accommodation of the workplace, or alternatives to vaccination such as testing, should be and have often been identified by courts, tribunals and arbitrators, as being a core element of the legality of mandates.[81 113 124 126] Mandates imposing unconditional vaccination, those ignoring the role of prior infection, and those ignoring a shifting risk/benefit balance depending on specific populations, should be considered suspect from a legal proportionality perspective.

When members of the public perceive mandates to be ethically and legally problematic and in violation of established norms of informed consent and proportionality, this will erode trust in public health and scientific institutions and even courts that endorsed or actively promoted such policies. This presents a challenging paradox for experts and authorities: will pro-mandate scientists and organisations come to acknowledge that mandates and passports were disproportionate policy responses? One key aspect of building trust in science and public health involves the open acknowledgement of when experts are wrong and when policies were misguided; however, it appears that many officials have doubled down in their narratives. This may undermine key ethical and legal criteria for policy and have damaging effects on the integrity of public health itself.

Erosion of trust in regulatory oversight

COVID-19 vaccines were developed in record time to meet an urgent public health need and have been accepted by billions of people, preventing deaths, severe hospitalisation and long-term sequelae from SARS-CoV-2.[3–6] COVID-19 vaccines have also generated at least $100 billion profit for pharmaceutical companies, especially Pfizer.[127] Has the acceptance of mandates and passports—and the rhetoric around 'anti-vaxxers'—contributed to a cultural shift in norms of scientific and corporate transparency and accountability?

Governments have refused to disclose the details of contracts with manufacturers, including for additional doses or 'next-generation' vaccines.[99] Vaccines are typically not approved until 2 years of follow-up data are gathered,[2] but given the urgency of the COVID-19 pandemic and international harmonisation of new agile regulations, the novel mRNA COVID-19 vaccines were placed into emergency use in Europe and North America in late 2020.[128] There is concern that, in the fog of crisis, vaccine policy is being driven by vaccine manufacturers rather than independent scientific and regulatory review. For

example, in April 2021, Moderna informed their investors that they were expecting a robust 'variant booster market' as a source of profits. Similarly, Pfizer CEO Albert Bourla suggested that a fourth dose of vaccine would be necessary, without any clinical trial data or independent evaluation that the benefits of subsequent doses outweigh any risks, nor consideration of the changing clinical dynamics with the Omicron variant.[118] This only adds to distrust over decision-making around vaccine use and ensuing mandates. The public is aware of the history of corporate pharmaceutical malfeasance and criminal and civil settlements in the billions of dollars, including with Pfizer, in part resulting from marketing practices and misrepresentation of safety and efficacy of medicines.[50 51 129]

The nature of mandates, passports and restrictions has increased public demands for scientific accountability and transparency—shown to be fundamental to building long-term confidence in vaccination.[130] This has increased the need to diligently track all safety signals for adverse effects in specific demographics[131] and explore trends in overall population mortality and potential non-specific effects.[132] However, the original clinical trial data remain unavailable for independent scientific scrutiny[50 51] ; a whistleblower raised important concerns about data integrity and regulatory oversight practices at a contract company helping with Pfizer's clinical trials in the USA.[133] After a Freedom of Information Act (FOIA) request by a civil society group (see: https://phmpt.org), the US Food and Drug Administration (FDA) requested (ultimately denied by a federal judge) 75 years to fully release internal documents and communications related to the regulatory process between FDA and Pfizer. In September 2021, an FDA advisory committee voted 16–2 against boosting healthy young adults in the USA but was over-ridden by the White House and CDC, leading to the resignation of two top FDA vaccine experts.[118] Such efforts have only increased the perception that regulatory agencies are 'captured' by industry and would conveniently ignore a higher than usual adverse effect ratio to control the pandemic. Concerns have been raised about the lack of due process in vaccine injury compensation claims for the COVID-19 vaccines,[100] which are to be borne by governments and not pharmaceutical companies. A video of a US congressional roundtable on COVID-19 vaccine adverse events with medically confirmed vaccine-injured individuals from the original clinical trials, a US military clinician and Peter Doshi (senior editor of the BMJ) was permanently removed by YouTube.[134] These practices do not reinforce confidence that authorities are being transparent or applying optimal standards for regulatory safety, efficacy and quality for these novel vaccines—standards which should arguably be more stringent given the legal precedent for mandates and passports.

CONCLUSION

The adoption of new vaccination policies has provoked backlash, resistance and polarisation. It is important to emphasise that these policies are not viewed as 'incentives' or 'nudges' by substantial proportions of populations[25–28 41 45] especially in marginalised, underserved or low COVID-19-risk groups. Denying individuals education, livelihoods, medical care or social life unless they get vaccinated—especially in light of the limitations with the current vaccines—is arguably in tension with constitutional and bioethical principles, especially in liberal democracies.[30–33] While public support consolidated behind these policies in many countries, we should acknowledge that ethical frameworks were designed to ensure that rights and liberties are respected even during public health emergencies.

Vaccination policies can be an important tool in the promotion of the right to health, but they need to be proportionate and designed to achieve a clearly defined goal. Some of those supporting current restrictions based on vaccination status[116] seem to accept too easily that these measures are indeed proportionate; that they are not more restrictive than necessary; that they are effective in preventing transmission and protecting the healthcare system from collapse; and that there are no options available other than punitive mandates, passports and segregated restrictions. As illustrated above, we believe that current vaccine policies have failed on these fronts and are no longer fit for purpose.

We encourage social and behavioural scientists, bioethicists, epidemiologists, legal scholars, and others to assess the benefits and harms of COVID-19 vaccination policies, along with wider open multidisciplinary discussion and debate. Empirical assessments may or may not validate the concerns presented in this paper—but their generation is critical in engagement with politicians, scientists, and organisations to reconsider current policies affecting those who remain unvaccinated as well as those who vaccinated due to threats and pressure. COVID-19 will not be the last public health emergency and it remains critical that we understand the reasons these approaches were adopted and provide robust evidence to improve future policymaking in times of health emergencies.[135] If not, the proclivity for mandates, passports, restrictions, fines and punishments is likely to become an accepted policy response for the next pandemic irrespective of whether such policies are truly effective, ethical and socially harmful.

If current policies are to continue, public health-associated bureaucracies and society will have to increase coercion to address current and future resistance and, in the process, come to leverage strategies more consistent with policing than public health. We may also see political forces double down and use people who have chosen not to get vaccinated as a collective, psychological and political tool to scapegoat and reinforce a false notion of safety among vaccinated people as they yearn to resume social and economic life. Policymakers should

reflect on the necessity of enforcing what is essentially a new two-tier, segregated social system and how this will affect different social groups now and into the future—behaviourally, politically and socioeconomically—as well as the impact of such policies on the integrity of science and public health itself.

There are other options to address the pandemic and it is not too late to return to non-coercive public health measures, including pro-social language and community leadership for vaccination, especially to protect high-risk groups.[7] Future investments in public health capacity, especially health providers who build relationships of trust working in communities, will be essential to engage in positive reforms. Improving data transparency, media independence and broad public debate and scrutiny about COVID-19 vaccine policies will also be essential to maintain population trust, help people better understand the risks and benefits of the continued use of current vaccines, and to inform research on improvements and future policies.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults

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ABSTRACT

Introduction: In 2020, prior to COVID-19 vaccine rollout, the Brighton Collaboration created a priority list, endorsed by the World Health Organization, of potential adverse events relevant to COVID-19 vaccines. We adapted the Brighton Collaboration list to evaluate serious adverse events of special interest observed in mRNA COVID-19 vaccine trials.

Methods: Secondary analysis of serious adverse events reported in the placebo-controlled, phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines in adults (NCT04368728 and NCT04470427), focusing analysis on Brighton Collaboration adverse events of special interest.

Results: Pfizer and Moderna mRNA COVID-19 vaccines were associated with an excess risk of serious adverse events of special interest of 10.1 and 15.1 per 10,000 vaccinated over placebo baselines of 17.6 and 42.2 (95 % CI −0.4 to 20.6 and −3.6 to 33.8), respectively. Combined, the mRNA vaccines were associated with an excess risk of serious adverse events of special interest of 12.5 per 10,000 vaccinated (95 % CI 2.1 to 22.9); risk ratio 1.43 (95 % CI 1.07 to 1.92). The Pfizer trial exhibited a 36 % higher risk of serious adverse events in the vaccine group; risk difference 18.0 per 10,000 vaccinated (95 % CI 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of serious adverse events in the vaccine group: risk difference 7.1 per 10,000 (95 % CI –23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of serious adverse events in mRNA vaccine recipients: risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39).

Discussion: The excess risk of serious adverse events found in our study points to the need for formal harm-benefit analyses, particularly those that are stratified according to risk of serious COVID-19 outcomes. These analyses will require public release of participant level datasets.

1. Introduction

In March 2020, the Brighton Collaboration and the Coalition for Epidemic Preparedness Innovations partnership, Safety Platform for Emergency vACcines (SPEAC), created and subsequently updated a "priority list of potential adverse events of special interest relevant to COVID-19 vaccine trials." [1] The list comprises adverse events of special interest (AESIs) based on the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based on animal models, and COVID-19 specific immunopathogenesis. [1] The Brighton Collaboration is a global authority on the topic of vaccine safety and in May 2020, the World Health Organization's Global Advisory Committee on Vaccine Safety endorsed and recommended the reporting of AESIs based on this priority list. To our knowledge, however, the list has not been applied to serious adverse events in randomized trial data.

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We sought to investigate the association between FDA-authorized mRNA COVID-19 vaccines and serious adverse events identified by the Brighton Collaboration, using data from the phase III randomized, placebo-controlled clinical trials on which authorization was based. We consider these trial data against findings from post-authorization observational safety data. Our study was not designed to evaluate the overall harm-benefit of vaccination programs so far. To put our safety results in context, we conducted a simple comparison of harms with benefits to illustrate the need for formal harm-benefit analyses of the vaccines that are stratified according to risk of serious COVID-19 outcomes. Our analysis is restricted to the randomized trial data, and does not consider data on post-authorization vaccination program impact. It does however show the need for public release of participant level trial datasets.

2. Methods

Pfizer and Moderna each submitted the results of one phase III randomized trial in support of the FDA's emergency use authorization of their vaccines in adults. Two reviewers (PD and RK) searched journal publications and trial data on the FDA's and Health Canada's websites to locate serious adverse event results tables for these trials. The Pfizer and Moderna trials are expected to follow participants for two years. Within weeks of the emergency authorization, however, the sponsors began a process of unblinding all participants who elected to be unblinded. In addition, those who received placebo were offered the vaccine. These self-selection processes may have introduced nonrandom differences between vaccinated and unvaccinated participants, thus rendering the post-authorization data less reliable. Therefore, to preserve randomization, we used the interim datasets that were the basis for emergency authorization in December 2020, approximately 4 months after trials commenced.

The definition of a serious adverse event (SAE) was provided in each trial's study protocol and included in the supplemental material of the trial's publication. [2–4] Pfizer and Moderna used nearly identical definitions, consistent with regulatory expectations. An SAE was defined as an adverse event that results in any of the following conditions: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment.

In addition to journal publications, we searched the websites of the FDA (for advisory committee meeting materials) and Health Canada (for sections of the dossier submitted by sponsors to the regulator). [5] For the FDA website, we considered presentations by both the FDA and the sponsors. [6] Within each of these sources, we searched for SAE results tables that presented information by specific SAE type; we chose the most recent SAE table corresponding to the FDA's requirement for a safety median follow-up time of at least 2 months after dose 2.

For each trial, we prepared blinded SAE tables (containing SAE types without results data). Using these blinded SAE tables, two clinician reviewers (JF and JE) independently judged whether each SAE type was an AESI. SAE types that matched an AESI term verbatim, or were an alternative diagnostic name for an AESI term, were included as an AESI. For all other SAE types, the reviewers independently judged whether that SAE type was likely to have been caused by a vaccine-induced AESI, based on a judgment considering the disease course, causative mechanism, and likelihood of the AESI to cause the SAE type. Disagreements were resolved through consensus; if consensus could not be reached, a third clinician reviewer (PW) was used to create a majority opinion. For each included SAE, we recorded the corresponding Brighton Collaboration AESI category and organ system. When multiple AESIs could potentially cause the same SAE, the reviewers selected the AESI that they judged to be the most likely cause based on classical clinical presentation of the AESI.

We used an AESI list derived from the work of Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project. This project created an AESI list which categorizes AESIs into three categories: those included because they are seen with COVID-19, those with a proven or theoretical association with vaccines in general, and those with proven or theoretical associations with specific vaccine platforms. The first version was produced in March 2020 based on experience from China. Following the second update (May 2020), the WHO Global Advisory Committee on Vaccine Safety (GACVS) adopted the list, and Brighton commenced a systematic review process "to ensure an ongoing understanding of the full spectrum of COVID-19 disease and modification of the AESI list accordingly." [7] This resulted in three additional AESIs being added to the list in December 2020. The subsequent (and most recent fourth) update did not result in any additional AESIs being added to the list. [1].

We matched SAEs recorded in the trial against an expanded list of AESIs created by combining Brighton's SPEAC COVID-19 AESI list with a list of 29 clinical diagnoses Brighton identified as "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list." [7] Sensitivity analysis was used to determine whether use of the original versus expanded list altered our results.

Risk ratios and risk differences between vaccine and placebo groups were calculated for the incidence of AESIs and SAEs. We excluded SAEs that were known efficacy outcomes (i.e. COVID-19), consistent with the approach Pfizer (but not Moderna) used in recording SAE data. The Pfizer study trial protocol states that COVID-19 illnesses and their sequelae consistent with the clinical endpoint definition were not to be reported as adverse events, "even though the event may meet the definition of an SAE." [8] For unspecified reasons, Moderna included efficacy outcomes in their SAE tables, effectively reporting an all-cause SAE result. Because we did not have access to individual participant data, to account for the occasional multiple SAEs within single participants, we reduced the effective sample size by multiplying standard errors in the combined SAE analyses by the square root of the ratio of the number of SAEs to the number of patients with an SAE. This adjustment increased standard errors by 10 % (Pfizer) and 18 % (Moderna), thus expanding the interval estimates. We estimated combined risk ratios and risk differences for the two mRNA vaccines by averaging over the risks using logistic regression models which included indicators for trial and treatment group.

We used a simple harm-benefit framework to place our results in context, comparing risks of excess serious AESIs against reductions in COVID-19 hospitalization.

3. Results

Serious adverse event tables were located for each of the vaccine trials submitted for EUA in adults (age 16 + for Pfizer, 18 + for Moderna) in the United States: Pfizer-BioNTech COVID-19 vaccine BNT162b2 (NCT04368728) [2,9,10] and Moderna COVID-19 vaccine mRNA-1273 (NCT04470427). [3,11,12] (Table 1).

3.1. Reporting windows and serious adverse events

Moderna reported SAEs from dose 1 whereas Pfizer limited reporting from dose 1 to 1 month after dose 2. Both studies

Table 1
Data sources for phase III trials.

Trial	Data cutoff date	Journal articles	FDA sources	Health Canada sources
Pfizer trial in ages 16 and above (NCT04368728)	14 Nov 2020 (supported Dec 2020 EUA)	Aggregate data only	**Table 23 in sponsor briefing document**	**Table 55 in sponsor document C4591001 Final Analysis Interim Report Body**
Moderna trial in ages 18 and above (NCT04470427)	25 Nov 2020 (supported Dec 2020 EUA)	Table S11 in publication	Table 27 in sponsor briefing document	**Table 14.3.1.13.3 in sponsor document mRNA-1273-P301 Unblinded Safety Tables Batch 1 (DS2)**

Note: bolded font indicates dataset chosen for analysis; EUA = Emergency Use Authorization.

reported all data at the time of data cutoff (14 Nov 2020 for Pfizer, 25 Nov 2020 for Moderna). 17 SAEs that were efficacy endpoints were removed from the Moderna trial (16 "COVID-19" SAEs and 1 "COVID-19 pneumonia" SAE). One such efficacy endpoint meeting the definition of a SAE was removed from the Pfizer trial ("SARS-CoV-2 test positive" SAE).

The Pfizer trial exhibited a 36 % higher risk of serious adverse events in vaccinated participants in comparison to placebo recipients: 67.5 per 10,000 versus 49.5 per 10,000; risk difference 18.0 per 10,000 vaccinated participants (95 % compatibility[1] interval 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of SAEs in vaccinated individuals compared to those receiving placebo: 136 per 10,000 versus 129 per 10,000; risk difference 7.1 per 10,000 (95 % CI −23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of SAEs in mRNA vaccine recipients than placebo recipients: 98 per 10,000 versus 85 per 10,000; risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39). **(**Table 2**)**.

3.2. Serious adverse events of special interest

Regarding whether each SAE type was included on the SPEAC derived AESI list, agreement between the two independent clinician reviewers was 86 % (281/325); 40 of the 44 disagreements were resolved through consensus, and only four disagreements necessitated a third clinician reviewer. **Supplemental** Table 1 includes a full list of included and excluded SAEs across both trials.

In the Pfizer trial, 52 serious AESI (27.7 per 10,000) were reported in the vaccine group and 33 (17.6 per 10,000) in the placebo group. This difference corresponds to a 57 % higher risk of serious AESI (RR 1.57 95 % CI 0.98 to 2.54) and a risk difference of 10.1 serious AESI per 10,000 vaccinated participants (95 % CI −0.4 to 20.6). In the Moderna trial, 87 serious AESI (57.3 per 10,000) were reported in the vaccine group and 64 (42.2 per 10,000) in the placebo group. This difference corresponds to a 36 % higher risk of serious AESI (RR 1.36 95 % CI 0.93 to 1.99) and a risk difference of 15.1 serious AESI per 10,000 vaccinated participants (95 % CI −3.6 to 33.8). Combining the trials, there was a 43 % higher risk of serious AESI (RR 1.43; 95 % CI 1.07 to 1.92) and a risk difference of 12.5 serious AESI per 10,000 vaccinated participants (95 % CI 2.1 to 22.9). **(**Table 2**)**.

Of the 236 serious AESIs occurring across the Pfizer and Moderna trials, 97 % (230/236) were adverse event types included as AESIs because they are seen with COVID-19. In both Pfizer and Moderna trials, the largest excess risk occurred amongst the Brighton category of coagulation disorders. Cardiac disorders have been of central concern for mRNA vaccines; in the Pfizer trial more cardiovascular AESIs occurred in the vaccine group than in the placebo group, but in the Moderna trial the groups differed by only 1 case. **(**Tables 3 and 4**)**.

[1] A compatibility interval is identical to a confidence interval, but relabeled to emphasize that it is not a Bayesian posterior interval (as is improperly suggested by the "confidence" label).[13,14].

3.3. Sensitivity analysis

As a sensitivity analysis, we restricted the serious AESI analysis to those AESIs listed in SPEAC's COVID-19 AESI list (i.e. separating out Brighton's list of 29 clinical diagnoses "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list.") This reduced the total number of AESIs across the two trials by 48 (35 vaccine group, 13 placebo group). There was still a higher risk of serious AESI when limited to the SPEAC COVID-19 AESI list, but the magnitude of the excess (in both relative and absolute terms) was smaller than when using the larger AESI list. **(Supplemental** Table 2**)**.

3.4. Harm-benefit considerations

In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants). [3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants).

4. Comparison with FDA reviews

In their review of SAEs supporting the authorization of the Pfizer and Moderna vaccines, the FDA concluded that SAEs were, for Pfizer, "balanced between treatment groups," [15] and for Moderna, were "without meaningful imbalances between study arms." [16] In contrast to the FDA analysis, we found an excess risk of SAEs in the Pfizer trial. Our analysis of Moderna was compatible with FDA's analysis, finding no meaningful SAE imbalance between groups.

The difference in findings for the Pfizer trial, between our SAE analysis and the FDA's, may in part be explained by the fact that the FDA analyzed the total number of participants experiencing any SAE, whereas our analysis was based on the total number of SAE events. Given that approximately twice as many individuals in the vaccine group than in the placebo group experienced multiple SAEs (there were 24 more events than participants in the vaccine group, compared to 13 in the placebo group), FDA's analysis of only the incidence of participants experiencing any SAE would not reflect the observed excess of multiple SAEs in the vaccine group.

A more important factor, however, may be that FDA's review of non-fatal SAEs used a different analysis population with different follow-up windows. The FDA reported 126 of 21,621 (0.6 %) of vaccinated participants experienced at least one SAE at data cutoff compared to 111 of 21,631 (0.5 %) of placebo participants. In contrast, our analysis found 127 SAEs among 18,801 vaccine recipients versus 93 SAEs among 18,785 placebo recipients. [15] While summary results for the population we analyzed was provided in a table, FDA did not report an analysis of them. The substantially larger denominators in FDA's analysis (5,666 more participants) reflect the fact that their analysis included all individuals receiving at least one dose (minus 196 HIV-positive participants), irrespec-

Table 2
Serious adverse events.

Trial	Total events (events per 10,000 participants)[a] Vaccine	Placebo	Risk difference per 10,000 participants (95 % CI)[e]	Risk ratio (95 % CI)[e]
Serious adverse events				
Pfizer[b]	127 (67.5)	93 (49.5)	18.0 (1.2 to 34.9)	1.36 (1.02 to 1.83)
Moderna[c,d]	206 (135.7)	195 (128.6)	7.1 (−23.2 to 37.4)	1.06 (0.84 to 1.33)
Combined[f]	333 (98.0)	288 (84.8)	13.2 (-3.2 to 29.6)	1.16 (0.97 to 1.39)
Serious adverse events of special interest				
Pfizer	52 (27.7)	33 (17.6)	10.1 (-0.4 to 20.6)	1.57 (0.98 to 2.54)
Moderna	87 (57.3)	64 (42.2)	15.1 (-3.6 to 33.8)	1.36 (0.93 to 1.99)
Combined[f]	139 (40.9)	97 (28.6)	12.5 (2.1 to 22.9)	1.43 (1.07 to 1.92)

[a] Denominators for Pfizer were 18,801 in the vaccine group and 18,785 in the placebo group, and for Moderna were 15,185 in the vaccine group and 15,166 in the placebo group.
[b] Pfizer excluded efficacy outcomes from its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). However, at least one SAE appears to have been inadvertently included, which we removed from our calculations (“SARS-CoV-2 test positive”: 0 vaccine group; 1 placebo group).
[c] Moderna included efficacy outcomes in its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). We removed efficacy SAEs outcomes that could be identified: “COVID-19” and “COVID-19 pneumonia.” Lacking access to participant level data, SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in this analysis.
[d] “All SAEs” for Moderna was calculated using the “Number of serious AEs” row in Moderna’s submission to FDA.[11].
[e] Standard errors used to estimate 95% CIs were inflated by the factor $\sqrt{}$[#SAE]/[#patients with SAE] to account for multiple SAE within patients.
[f] The combined risk differences and risk ratios were computed from the fitted logistic regression models and so may not exactly equal comparisons computed from the first two columns.

Table 3
Serious AESIs, Pfizer trial.

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with immunization in general						
Anaphylaxis	1	1	0.5	0.5	0.0	1.00
Association with specific vaccine platform(s)						
Encephalitis/encephalomyelitis	0	2	0.0	1.1	−1.1	0.00
Seen with COVID-19						
Acute kidney injury	2	0	1.1	0.0	1.1	N/A
Acute liver injury	0	1	0.0	0.5	−0.5	0.00
Acute respiratory distress syndrome	2	1	1.1	0.5	0.5	2.00
Coagulation disorder	16	10	8.5	5.3	3.2	1.60
Myocarditis/pericarditis	2	1	1.1	0.5	0.5	2.00
Other forms of acute cardiac injury	16	12	8.5	6.4	2.1	1.33
Subtotal	39	28	20.7	14.9	5.8	1.39
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	4	1	2.1	0.5	1.6	4.00
Cholecystitis	4	2	2.1	1.1	1.1	2.00
Colitis/Enteritis	1	1	0.5	0.5	0.0	1.00
Diarrhea	1	0	0.5	0.0	0.5	N/A
Hyperglycemia	1	1	0.5	0.5	0.0	1.00
Pancreatitis	1	0	0.5	0.0	0.5	N/A
Psychosis	1	0	0.5	0.0	0.5	N/A
Subtotal	13	5	6.9	2.7	4.3	2.60
Total	**52**	**33**	**27.7**	**17.6**	**10.1**	**1.57**

tive of the duration of post-injection follow-up time. In contrast, our analysis was based on the study population with median follow-up $\geq$ 2 months after dose 2 (minus 120 HIV-positive participants), of which 98.1 % had received both doses. [2,17] The FDA’s analysis of SAEs thus included thousands of additional participants with very little follow-up, of which the large majority had only received 1 dose.

4.1. Comparison with post-authorization studies

Although the randomized trials offer high level evidence for evaluating causal effects, the sparsity of their data necessitates that harm-benefit analyses also consider observational studies. Since their emergency authorization in December 2020, hundreds of millions of doses of Pfizer and Moderna COVID-19 vaccines have been administered and post-authorization observational data offer a complementary opportunity to study AESIs. Post-authorization observational safety studies include cohort studies (which make use of medical claims or electronic health records) and disproportionality analyses (which use spontaneous adverse event reporting systems). In July 2021, the FDA reported detecting four potential adverse events of interest: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation following Pfizer’s vaccine based on medical claims data in older Americans. [18] Three of these four serious adverse event types would be categorized as coagulation disorders, which is the Brighton AESI category that exhibited the largest excess risk in the vaccine group in both the Pfizer and Moderna trials. FDA stated it would further investigate the findings but at the time of our writing has not issued an update. Similarly, spontaneous-reporting systems have registered serious adverse reactions including anaphylaxis (all COVID-19 vaccines), thrombocytopenia syndrome among premenopausal females (Janssen vaccine), and myocarditis and pericarditis among younger males (Pfizer and Moderna vaccines). [19,20].

Using data from three postmarketing safety databases for vaccines (VAERS, EudraVigilance, and VigiBase), disproportionality studies have reported excess risks for many of the same SAE types as in

Table 4
Serious AESIs, Moderna trial.

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with specific vaccine platform(s)						
Bell's Palsy	1	0	0.7	0.0	0.7	N/A
Encephalitis/encephalomyelitis	1	0	0.7	0.0	0.7	N/A
Seen with COVID-19						
Acute kidney injury	1	3	0.7	2.0	−1.3	0.33
Acute liver injury	1	0	0.7	0.0	0.7	N/A
Acute respiratory distress syndrome	7	4	4.6	2.6	2.0	1.75
Angioedema	0	2	0.0	1.3	−1.3	0.00
Coagulation disorder	20	13	13.2	8.6	4.6	1.54
Generalized Convulsions	2	0	1.3	0.0	1.3	N/A
Myelitis	0	1	0.0	0.7	−0.7	0.00
Myocarditis/pericarditis	4	5	2.6	3.3	−0.7	0.80
Other forms of acute cardiac injury	26	26	17.1	17.1	0.0	1.00
Other rash	1	1	0.7	0.7	0.0	1.00
Rhabdomyolysis	0	1	0.0	0.7	−0.7	0.00
Single Organ Cutaneous Vasculitis	1	0	0.7	0.0	0.7	N/A
Subtotal	65	56	42.8	36.9	5.9	1.16
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	1	0	0.7	0.0	0.7	N/A
Arthritis	3	1	2.0	0.7	1.3	3.00
Cholecystitis	4	0	2.6	0.0	2.6	N/A
Colitis/Enteritis	6	3	4.0	2.0	2.0	2.00
Diarrhea	2	1	1.3	0.7	0.7	2.00
Hyperglycemia	1	0	0.7	0.0	0.7	N/A
Hyponatremia	1	1	0.7	0.7	0.0	1.00
Pancreatitis	2	0	1.3	0.0	1.3	N/A
Pneumothorax	0	1	0.0	0.7	−0.7	0.00
Psychosis	1	1	0.7	0.7	0.0	1.00
Thyroiditis	1	0	0.7	0.0	0.7	N/A
Subtotal	22	8	14.5	5.3	9.2	2.75
Total	**87**	**64**	**57.3**	**42.2**	**15.1**	**1.36**

the present study. [21–23] For example, a study using VAERS and EudraVigilance comparing the disproportionality of adverse event reports between the influenza vaccine versus the mRNA COVID-19 vaccines reported excess risks for the following Brighton AESIs: cardiovascular events, coagulation events, hemorrhages, gastrointestinal events, and thromboses. [22] While CDC published a protocol[24] in early 2021 for using proportional reporting ratios for signal detection in the VAERS database, results from the study have not yet been reported. [25] Among self-controlled case series, one reported a rate ratio of 1.38 (95 % CI 1.12–1.71) for hemorrhagic stroke following Pfizer vaccine, [26] another reported 0.97 (95 % CI 0.81–1.15), [27] while a cohort study[28] reported 0.84 (95 % CI 0.54–1.27).

5. Discussion

Using a prespecified list of AESI identified by the Brighton Collaboration, higher risk of serious AESI was observed in the mRNA COVID-19 vaccine group relative to placebo in both the Pfizer and Moderna adult phase III trials, with 10.1 (Pfizer) and 15.1 (Moderna) additional events for every 10,000 individuals vaccinated. Combined, there was a risk difference of 12.5 serious AESIs per 10,000 individuals vaccinated (95 % CI 2.1 to 22.9). These results raise concerns that mRNA vaccines are associated with more harm than initially estimated at the time of emergency authorization. In addition, our analysis identified a 36 % higher risk of serious adverse events in vaccinated participants in the Pfizer trial: 18.0 additional SAEs per 10,000 vaccinated (95 % CI 1.2 to 34.9). Consistent with the FDA evaluation, our analysis found no clear difference in SAEs between groups in the Moderna trial.

Results between the Pfizer and Moderna trials were similar for the AESI analysis but exhibited substantial variation in the SAE analysis. Caution is needed in interpreting this variation as it may be substantially explained by differences in SAE recording practices in the trials rather than differences in actual vaccine harm profiles. For reasons that are not documented in the trial protocol, Moderna included efficacy outcomes in its SAE tabulations, while Pfizer excluded them. As a result, Moderna's SAE table did not present a traditional SAE analysis but rather an all-cause SAE analysis. The FDA analysis of the Moderna trial presented an all-cause SAE analysis, which estimates total vaccine effects on SAEs, including effects transmitted via effects on COVID-19. It did not however present a traditional SAE analysis with efficacy endpoints removed, which attempts to estimate only the direct effects on SAEs. While our analysis attempted to perform a traditional SAE analysis by excluding efficacy SAEs (serious COVID-19 and its sequelae), our effort was hindered because we did not have access to patient level data. Easily recognizable efficacy SAEs ("COVID-19", "COVID-19 pneumonia," and "SARS-CoV-2 test positive") could be removed, but many participants who experienced a COVID-19 SAE likely experienced multiple other SAEs (e.g. pneumonia, hypoxia, and thrombotic events) which could not be identified and therefore remain included in our analysis. Of 17 total efficacy SAEs (16 "COVID-19" and 1 "COVID-19 pneumonia") removed from our analysis of the Moderna trial, 16 were in the placebo arm. As a consequence, the background SAE risk (risk in absence of COVID-19) would be overestimated by the Moderna placebo group, resulting in underestimation of the actual risk of SAEs and AESIs attributable to the vaccine in the Moderna comparisons as well as in the combined analysis. Access to patient-level data would allow adjustments for this problem.

Rational policy formation should consider potential harms alongside potential benefits. [29] To illustrate this need in the present context, we conducted a simple harm-benefit comparison using the trial data comparing excess risk of serious AESI against reductions in COVID-19 hospitalization. We found excess risk of serious AESIs to exceed the reduction in COVID-19 hospitalizations in both Pfizer and Moderna trials.

This analysis has the limitations inherent in most harm-benefit comparisons. First, benefits and harms are rarely exact equivalents, and there can be great variability in the degree of severity within both benefit and harm endpoints. For example, intubation and short hospital stay are not equivalent but both are counted in "hospitalization"; similarly, serious diarrhea and serious stroke are not equivalent but both are counted in "SAE." Second, individuals value different endpoints differently. Third, without individual participant data, we could only compare the number of individuals hospitalized for COVID-19 against the number of serious AESI events, not the number of participants experiencing any serious AESI. Some individuals experienced multiple SAEs whereas hospitalized COVID-19 participants were likely only hospitalized once, biasing the analysis towards exhibiting net harm. To gauge the extent of this bias, we considered that there were 20 % (Pfizer) and 34 % (Moderna) more SAEs than participants experiencing any SAE. As a rough sensitivity calculation, if we divide the Pfizer excess serious AESI risk of 10.1 by 1.20 it becomes 8.4 compared to a COVID-19 hospitalization risk reduction of 2.3; if we divide the Moderna excess serious AESI risk of 15.1 by 1.34 it becomes 11.3 compared to a COVID-19 hospitalization risk reduction of 6.4.

Harm-benefit ratios will be different for populations at different risk for serious COVID-19 and observation periods that differ from those studied in the trials. Presumably, larger reductions in COVID-19 hospitalizations would have been recorded if trial follow-up were longer, more SARS-CoV-2 was circulating, or if participants had been at higher risk of serious COVID-19 outcomes, shifting harm-benefit ratios toward benefit. Conversely, harm-benefit ratios would presumably shift towards harm for those with lower risk of serious COVID-19 outcomes--such as those with natural immunity, younger age or no comorbidities. Similarly, waning vaccine effectiveness, decreased viral virulence, and increasing degree of immune escape from vaccines might further shift the harm-benefit ratio toward harm. Large, randomized trials in contemporary populations could robustly answer these questions. Absent definitive trials, however, synthesis of multiple lines of evidence will be essential. [30,48,49].

Adverse events detected in the post-marketing period have led to the withdrawal of several vaccines. An example is intussusception following one brand of rotavirus vaccine: around 1 million children were vaccinated before identification of intussusception, which occurred in around 1 per 10,000 vaccinees. [31] Despite the unprecedented scale of COVID-19 vaccine administration, the AESI types identified in our study may still be challenging to detect with observational methods. Most observational analyses are based on comparing the risks of adverse events "observed" against a background (or "expected") risk, which inevitably display great variation, by database, age group, and sex. [32] If the actual risk ratio for the effect was 1.4 (the risk ratio of the combined AESI analysis), it could be quite difficult to unambiguously replicate it with observational data given concerns about systematic as well as random errors. [33–35].

In addition, disproportionality analyses following COVID-19 vaccination also have limitations, particularly with respect to the type of adverse events seen in our study. The majority of SAEs that contributed to our results are relatively common events, such as ischemic stroke, acute coronary syndrome, and brain hemorrhage. This complicates signal detection because clinical suspicion of an adverse vaccine reaction following an event commonly seen in clinical practice will be lower than for SAEs like myocarditis.[50] For this reason, clinical suspicion leading to the filing of an individual case safety report--may be far less common in the post-authorization setting than in the trials. At the same time, heightened awareness about COVID-19 vaccine SAEs can result in under and overreporting. Public health messages assuring vaccine safety may lower clinical suspicion of potential causal relationships, whereas messages about potential harms can conversely stimulate reports that otherwise may not have been made. These factors can lead to bias both directions, further complicating interpretation. In contrast to these problems, in the randomized trials used in this analysis, all SAEs were to be recorded, irrespective of clinical judgment regarding potential causality.

Although our analysis is secondary, reanalyses of clinical trial data have led to the detection of adverse events well after the market entry of major drugs such as rofecoxib and rosiglitazone. [36,37] Our analysis has an advantage over postmarketing observational studies in that the data are from blinded, placebo-controlled randomized trials vetted by the FDA, which were matched against a list of adverse events created before the availability of the clinical-trial results and designed for use in COVID-19 vaccine trials.

Our study has several important limitations. First, Pfizer's trial did not report SAEs occurring past 1 month after dose 2. This reporting threshold may have led to an undercounting of serious AESIs in the Pfizer trial. Second, for both studies, the limited follow up time prevented an analysis of harm-benefit over a longer period. Third, all SAEs in our analysis met the regulatory definition of a serious adverse event, but many adverse event types which a patient may themselves judge as serious may not meet this regulatory threshold. Fourth, decisions about which SAEs to include or exclude as AESIs requires subjective, clinical judgements in the absence of detailed clinical information about the actual SAEs. We encourage third party replication of our study, with access to complete SAE case narratives, to determine the degree to which these decisions affected our findings. For additional sensitivity analyses, such replication studies could also make use of other AESI lists, such as those prepared by FDA, [38–41] CDC, [24], Pfizer, [42], or a *de novo* AESI list derived from a list of COVID-19 complications understood to be induced via SARS-CoV-2's spike protein. [43,44].

A fifth important limitation is our lack of access to individual participant data, which forced us to use a conservative adjustment to the standard errors. The 95 % CIs[13,14] calculated are therefore only approximate because we do not know which patients had multiple events. Finally, as described above, in the Moderna analysis, the SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in our calculations. Because the vaccines prevent SAEs from COVID-19 while adding SAE risks of their own, this inclusion makes it impossible to separately estimate SAEs due to the vaccine from SAEs due to COVID-19 in the available Moderna data, as must be done to extrapolate harm-benefit to other populations. These study limitations all stem from the fact that the raw data from COVID-19 vaccine clinical trials are not publicly available. [45,46].

We emphasize that our investigation is preliminary, to point to the need for more involved analysis. The risks of serious AESIs in the trials represent only group averages. SAEs are unlikely to be distributed equally across the demographic subgroups enrolled in the trial, and the risks may be substantially less in some groups compared to others. Thus, knowing the actual demographics of those who experienced an increase in serious AESI in the vaccine group is necessary for a proper harm-benefit analysis. In addition, clinical studies are needed to see if particular SAEs can be linked to particular vaccine ingredients as opposed to unavoidable consequences of exposure to spike protein, as future vaccines could then be modified accordingly or sensitivities can be tested for in advance. In parallel, a systematic review and meta-analysis using individual participant data should be undertaken to address questions of harm-benefit in various demographic subgroups, particularly in those at low risk of serious complications from COVID-19. Finally, there is a pressing need for comparison of SAEs and harm-benefit for different vaccine types; some initial work has already begun in this direction. [47].

Full transparency of the COVID-19 vaccine clinical trial data is needed to properly evaluate these questions. Unfortunately, as we approach 2 years after release of COVID-19 vaccines, participant level data remain inaccessible. [45,46].

Author contributions

All authors had full access to all of the data in the study (available at https://doi.org/10.5281/zenodo.6564402), and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Doshi.
Analysis and interpretation: All authors.
Statistical analysis: Jones, Greenland.
Drafting of the manuscript: Fraiman, Doshi.
Critical revision of the manuscript for important intellectual content: All authors.

Data availability

All of the data in the study is available at https://doi.org/10.5281/zenodo.6564402

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical review statement

This research was confirmed to be Not Human Subjects Research (NHSR) by University of Maryland, Baltimore (HP-00102561).

Conflicts of interest

JF, JE, MJ, SG, PW, RK: none to declare. PD has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020) and is an editor at The BMJ. The views expressed here are those of the authors and do not necessarily reflect those of their employers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.036.

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Wireless technologies, non-ionizing electromagnetic fields and children: Identifying and reducing health risks

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Children today are conceived and live in a sea of wireless radiation that did not exist when their parents were born. The launch of the digital age continues to transform the capacity to respond to emergencies and extend global communications. At the same time that this increasingly ubiquitous technology continues to alter the nature of commerce, medicine, transport and modern life overall, its varied and changing forms have not been evaluated for their biological or environmental impacts. Standards for evaluating radiation from numerous wireless devices were first set in 1996 to avoid heating tissue and remain unchanged since then in the U.S. and many other nations. A wide range of evidence indicates that there are numerous non-thermal effects from wireless radiation on reproduction, development, and chronic illness. Many widely used devices such as phones and tablets function as two-way microwave radios, sending and receiving various frequencies of information-carrying microwave radiation on multiple simultaneously operating antennas. Expert groups advising governments on this matter do not agree on the best approaches to be taken. The American Academy of Pediatrics recommends limited screen time for children under the age of two, but more than half of all toddlers regularly have contact with screens, often without parental engagement. Young children of parents who frequently use devices as a form of childcare can experience delays in speech acquisition and bonding, while older children report feelings of disappointment due to 'technoference'—parental distraction due to technology. Children who begin using devices early in life can become socially, psychologically and physically addicted to the technology and experience withdrawal upon cessation. We review relevant experimental, epidemiological and clinical evidence on biological and other impacts of currently used wireless technology, including advice to include key questions at pediatric wellness checkups from infancy to young adulthood. We conclude that consistent with advice in pediatric radiology, an approach that recommends that microwave radiation exposures be As Low As Reasonably Achievable (ALARA) seems sensible and prudent, and that an independently-funded training, research and monitoring program should be carried out on the long term physical and psychological impacts of rapidly changing technological milieu, including ways to mitigate impacts through modifications in hardware and software. Current knowledge of electrohypersensitivity indicates the importance of reducing wireless exposures especially in schools and health care settings.

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Abbreviations: EMF, Electro-magnetic field; EMR, Electromagnetic Radiation; FCC, Federal Communications Commission (U.S.A.); ICNIRP, International Commission on Non-Ionizing Radiation Protection; IEEE, Institute of Electrical and Electronics Engineers; MF, Magnetic field; GSM, Global System for Mobile Communications; RFR, Radiofrequency radiation; SAR, Specific Absorption Rate (a measurement of the rate at which energy is absorbed into particular tissues, when exposed to RFR); SAM, Specific Anthropomorphic Mannequin (a physical model used to estimate SAR, based on a 220 pound male with a 12 pound head); HPG, Hypothalamic-Pituitary-Gonadal axis; HSP, Heat Shock Proteins; ORSAA, Oceania Radio Frequency Scientific Advisory Association; DECT, Digital Enhanced Cordless Telecommunications; ICBE-EMF, International Commission on the Biological Effects of Electromagnetic Fields; ELF-EMF, Extremely Low Frequency Electromagnetic Fields (0 − 3 kHz); CDMA, Code Division Multiple Access; UMTS, Universal Mobile Telecommunications System; LTE, Long Term Evolution; ROS, Reactive Oxygen Species

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Introduction. Children's exposures to wireless radiation are increasing rapidly

We live in the age of technological wonder, where the ability to respond to emergencies, engage in routine commerce, and even conduct warfare has been radically altered by wireless communications. At the same time, we are also in an age of technological imperatives; that is, the fact that something *can* technically be done has been misconstrued as an argument that this *should be done,* i.e., in favor of implementing that technology. Parents understand that—just because you *can* go skateboarding without a helmet and other protective equipment does not mean that is a *good* idea. From wireless baby monitors to the iPad potty for toddlers learning to use the toilet, Wi-Fi Barbie, tablets and cell phones, today's infants, toddlers, young children, and adolescents are surrounded by wireless technologies. None has been tested for their impacts on children. Especially when used at early stages of life these devices can interfere with social development, learning, and socialization. They also can have lifelong and potentially irreversible adverse biological effects.

"Children are not little adults and are disproportionately impacted by all environmental exposures, including cell phone radiation." American Academy of Pediatrics to the Federal Communications Commission (2013)[1]

Cell phones, tablets, and laptops typically operate as two-way microwave radios sending and receiving radiofrequency radiation (RFR) to and from internal and external antennas. Unchanged since 1996, RFR exposure standards for the use and operation of cell phones and other wireless devices rest on a crude physical model using an empty plastic ball for the head into which homogenous fluid is poured; this uniform medium cannot reflect the different densities and electromagnetic properties of developing physiology, morphology and tissues at different ages, and the greater vulnerability of infants, toddlers, and children. Health based standards have never been developed to take into account the vastly different technologies, uses and users employing devices today.

Although cellular communication systems and wireless technologies have demonstrated numerous direct benefits to society, they can also pose risks to the health and safety of the billions who are exposed to unnecessary levels of RFR throughout the life span. As demonstrated in this review, given the substantial experimental, epidemiological and clinical evidence that current levels of wireless radiation can be harmful, especially to the young, we concur with those experts who counsel that policies should be governed by the concept of ALARA—as low as reasonably achievable—while research continues to evolve.

The guiding principle of radiation safety, ALARA means avoiding exposure to radiation that does not have a direct benefit to you, even if the dose is small.[2]

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For more than a decade the American Academy of Pediatrics[3] and the American Academy of Child and Adolescent Psychiatry[4] advised that children age two and under have no screen time, yet infant and toddler use of devices is skyrocketing. That advice has now been modified to allow parentally supervised video calls for ages 18 to 24 months. The Pew Research Foundation surveyed parents in 2020 and 2021 and found that 8 out of 10 parents of a child who was age 11 or younger (81%) said their child had ever used a tablet computer in 2021 up from 68% in 2020[5]; 71% said their child had used a smartphone in 2021 (See Fig. 1). More recent numbers are sure to be higher, as the pandemic has led to increased reliance on digital

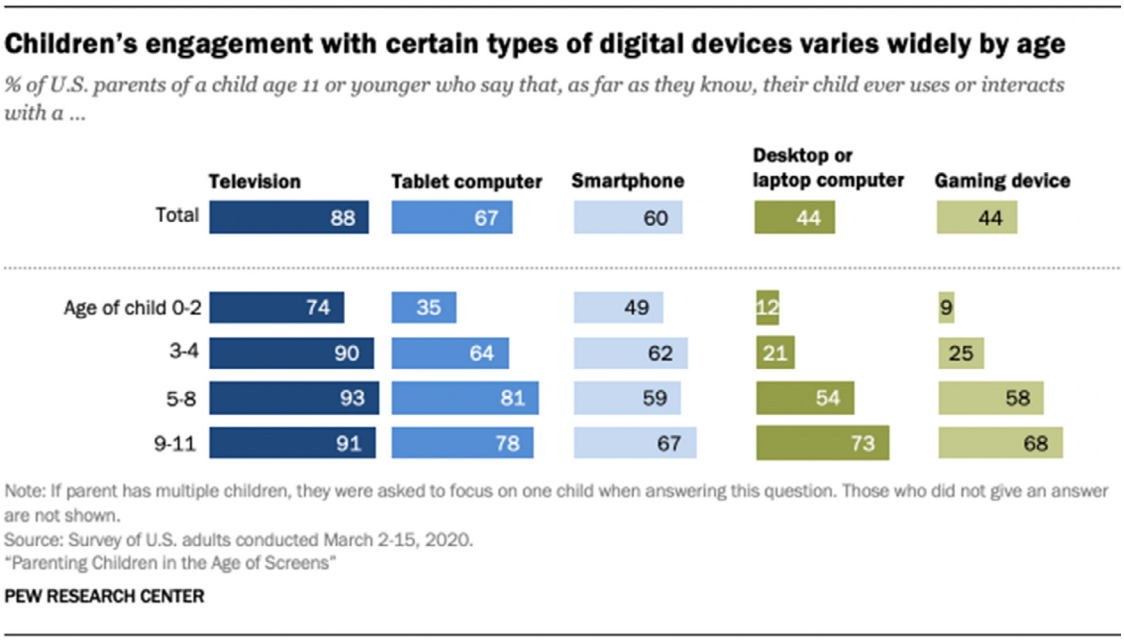

Fig. 1. Children's engagement with digital devices Survey 2020 by PEW Research Center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

devices. Reports of serious behavioral problems including problems with self-control, socialization, language acquisition and the like have been associated with device addiction; and internet gaming disorder is on the rise in all age groups.[6]

Decades of research on RFR (including microwaves) indicate that everyday exposure to wireless devices can impact the physical, emotional and psychological health and well-being of adults and children.[7] A growing number of independent researchers find that while regulators, such as the U.S. Federal Communications Commission (FCC) and International Commission on Non-ionizing Radiation (ICNIRP) currently consider "low-level" exposures safe; these levels do in fact place children's endocrine, reproductive, and immune systems at risk. These current regulatory limits are based on the assumption that over-heating by high power RFR is the only established health effect to be avoided. Nevertheless, numerous studies find that nonthermal levels of RFR can cause major adverse effects such as induction of reactive oxygen species (ROS), DNA damage, cardiomyopathy, carcinogenicity, sperm damage, memory damage, and neurological effects.[8] As with many other chemical and physical hazards, there is evidence indicating that greater detrimental impacts take place when exposures occur during critical phases of growth and development, including pregnancy.[9]

Since the 1990s, member states of the European Union and the FCC have looked to the ICNIRP[10] and the Institute of Electrical and Electronics Engineers (IEEE)[11] for risk assessments and guidance on occupational and public exposure to RFR from all sources. These groups assume that only thermal effects (excessive heating) are to be avoided. In contrast, the International Commission on Biological Effects of Electromagnetic Fields (ICBE-EMF)[12] and the Oceania Radiofrequency Scientific Assessment Association (ORSAA),[13,14] among others, reject the assumptions on which ICNIRP relies, providing detailed grounds for their positions.[15] Moreover, the former editor-in-chief of the journal *Bioelectromagnetics*[16] contends that standards for evaluating wireless phones and other devices have not kept pace with developments in technology finding that nonthermal effects do occur and therefore current FCC standards do not protect public health.

Regulations on both sides of the Atlantic have in common that they are founded on risk assessments conducted in the 1980s and early 1990s by industry scientists and their affiliates in the IEEE. Despite a considerable weight of evidence indicating serious biological and environmental impacts of nonthermal levels of RFR, the FCC and the ICNIRP risk assessments of non-ionizing radiation from phones and other devices have remained unchanged for decades.

Several thousand apps have been developed for infants and toddlers to use on phones, watches and tablets with no research on their long-term physical or psychological impacts.

When phones were first brought to market, children's cell phone use was unheard of. Today children are exposed to wireless radiation from cell phones as well as numerous sources in their homes, child care settings and schools as shown in Fig. 2. Several thousand apps have been developed for infants and toddlers to use on phones, watches and tablets with no research on their long-term physical or psychological impacts. (Fig. 2)

This article assembles key scientific information regarding why and how to reduce wireless exposures to the young, including limiting prenatal and neonatal exposures. The latest scientific and clinical studies on the biological impacts of wireless radiation and models of exposure are considered briefly in terms of unexplained trends in cancer, autism spectrum disorder, learning difficulties, attention deficit, behavioral and psychiatric disorders, and other increasing pediatric disorders. Finally, health professional and U.S. national policy developments aimed at protecting children from inappropriate and harmful exposures are presented, with specific recommendations and practices for safer use of technologies.

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Electromagnetic radiation and biological effects

Radio communications lie at the heart of the cell phone and wireless radiation revolution via electromagnetic "radio waves" or RFR.

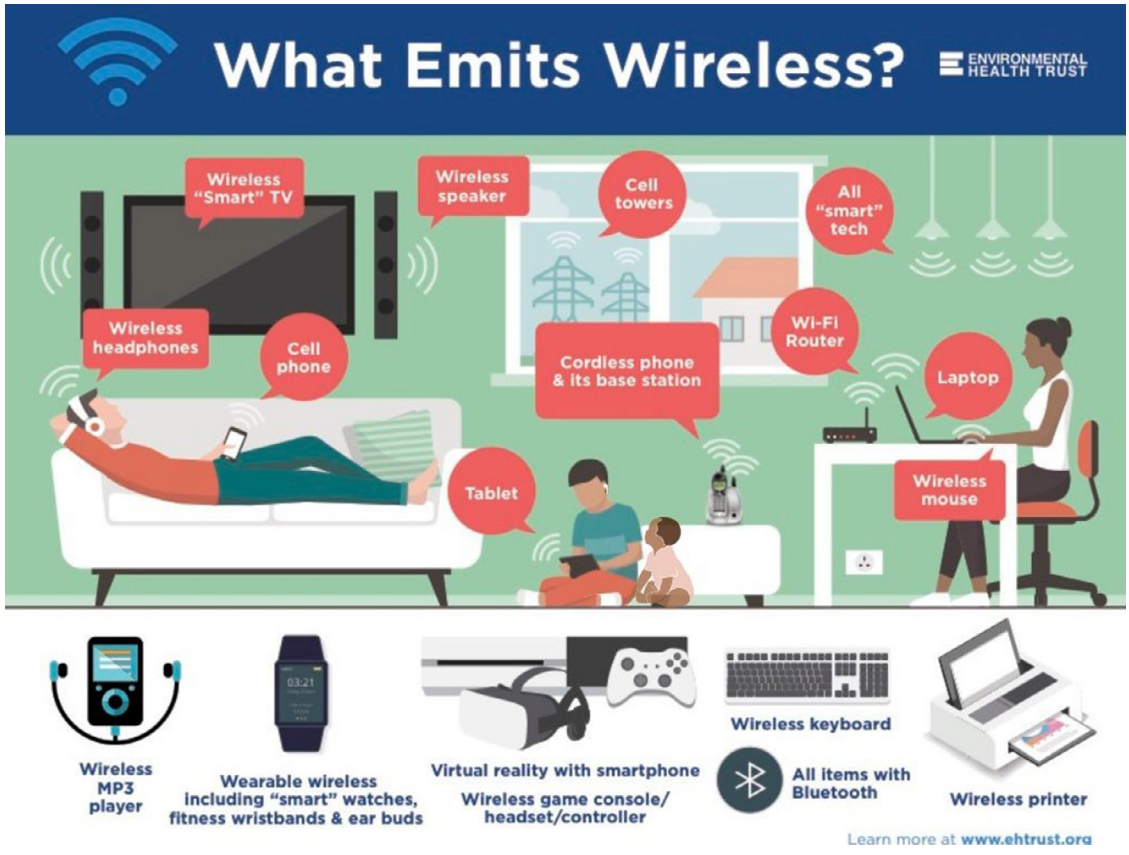

Fig. 2. Sources of wireless radiofrequency radiation in the home.

Electromagnetism

The theory of electromagnetism emerged in 1865 when James Clerk Maxwell unified Ampère's work on electricity, and Faraday's and others' work on magnetism into one unified theory.[17,18]

Simply put, an electric charge or the movement of electric charge (in electric currents through wires and devices) influences other charges or electrical currents at a distance. The influence, called a "field," results from attractive and repulsive forces between electrical charges. Positive and negative charges attract, while two charges of the same sign are forced apart. Of particular importance is how an oscillating charge creates a field that likewise oscillates, and this disturbance (called "radiation") propagates outward as a wave. Imagine a child flicking a skipping rope—the 'flick' propagates down the rope in the same fashion as the electric field propagates in the form of a wave. The theory was experimentally confirmed in 1887 by Heinrich Hertz.[19,20]

The duality of a wave is illustrated in Fig. 3. The oscillation can be described as a sine wave that depends both on the time and place of observation. The top frame of the Figure depicts the oscillation of the wave as seen by an observer standing in one place and looking over a period of time. One can imagine standing near the ocean and staring at a buoy as it undulates up and down as waves pass below. The bottom panel looks the same but depicts how at one instant in time the waves would look at every spot. Rather like standing on the same spot near the ocean and surveying open sea and all the waves before you. The characteristic features of the wave are its amplitude, A, its wavelength, λ (the distance between two sequential peaks) and its frequency, f (the number of oscillations per second, measured as Hertz [Hz] or reciprocal seconds [s^{-1}]). The relationship between these parameters, the cyclic frequency, ω, and the wavenumber, k, are illustrated in the Figure. Most importantly the multiplication of the frequency with the wavelength equals the speed of propagation, c.

Maxwell's theory predicted that the speed of light (visible light is a form of electromagnetic radiation) would be constant at 186,000 miles per second, confirming a measurement first made on earth (rather than by astronomical estimation as done by Ole Rømer and published in 1676[21]) by Hippolyte Fizeau in 1848.[22]

The frequencies of oscillation of electromagnetic waves can range from fractions of Hertz (a slow variation in field strength taking more than a second to complete) to billions of times a second. Each frequency can be exploited technologically in different ways and this is generally represented by the Electromagnetic Spectrum.

The electromagnetic spectrum

Physicians utilize electromagnetic radiation (EMR) in many forms. High-frequency, ionizing EMR is employed for diagnosis (e.g., X-ray and CAT scan imaging) and treatment (e.g., gamma-knife and other ionizing radiation treatments for cancer; non-ionizing ultraviolet radiation provides treatment of skin conditions such as psoriasis; infrared radiation is applied in physiotherapy and intensive care), while pulsed EMR are increasingly used in orthopedics and physical therapy. The electromagnetic spectrum includes visible light that forms a sliver of the spectrum (Fig. 4), with much of the remaining parts being invisible.

In public health, strong health and safety guidelines proscribe exposing infants and young children to the sun's rays beyond limited exposures. The problematic rays are found in the sun's ultraviolet (UV) light in the UVA and UVB frequency bands. While UVB is traditionally associated with direct DNA damage that leads to melanoma or less malignant forms of skin cancer, recent evidence indicates that UVA plays a greater role than previously assumed in the onset of skin cancers and can affect the immune system and other organs as well.[23] Other parts of the spectrum, especially that of blue light at 440 nanometers are used for their biological impacts on the skin to treat hyperbilirubinemia[24] by stimulating the production of di-hydroxy-vitamin D in the liver in jaundiced newborns. Untreated, the syndrome can result in bilirubin concentrations that can cause acute bilirubin encephalopathy and kernicterus− a permanent disabling neurologic condition. Blue light[25] is also known to interfere with sleep by impeding the production of melatonin, a natural hormone released by the pineal gland that is a potent anti-oxidant and free radical scavenger produced by sleeping in darkness.

Returning to the use of the spectrum for communication, the ability to transmit a travelling electrical field across space cannot itself establish a communication channel. For that to take place, information must be encoded into that transmission. The ability to code information on EMF was what Guglielmo Marconi

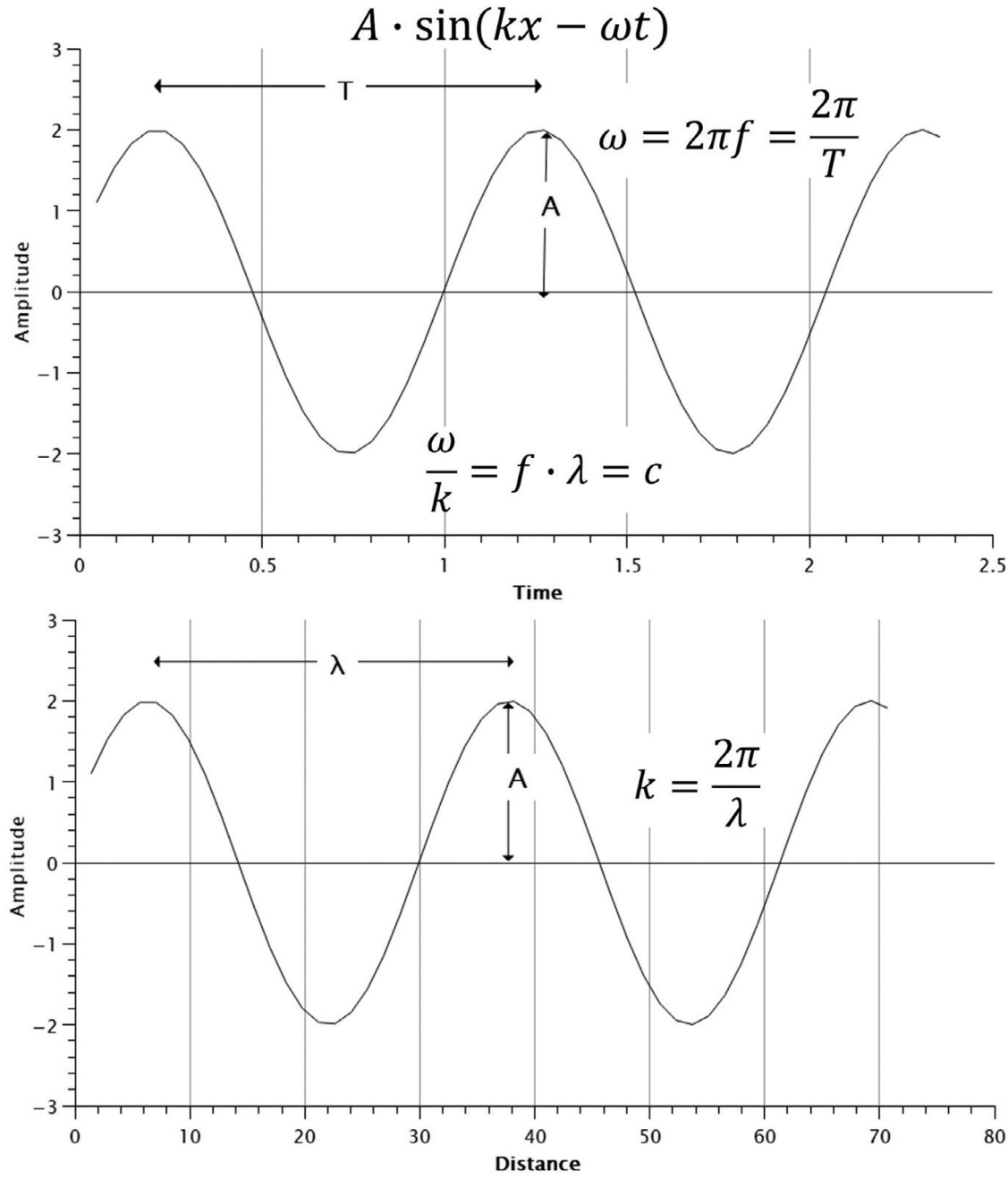

Fig. 3. Mathematical description of a continuous wave as a sine function. *A is the amplitude of the oscillation, f is the frequency, T is the time period for one complete oscillation, ω is the cyclic frequency (ω = 2pf) and k is the wave number.*

demonstrated in 1897[26] with his first transatlantic radio transmission.

Signals

The easiest way to encode information onto EMF is to turn the transmission on and off—Morse code in other words. Making a spark earned early Morse Code operators the moniker, "Sparky." Dots and dashes (a "digital" mode of communication) are comparable to the ones and zeros at the root of modern computing. More information can be transmitted by a careful modulation of the amplitude of the signal in proportion to the modulation of a sound, be it someone's

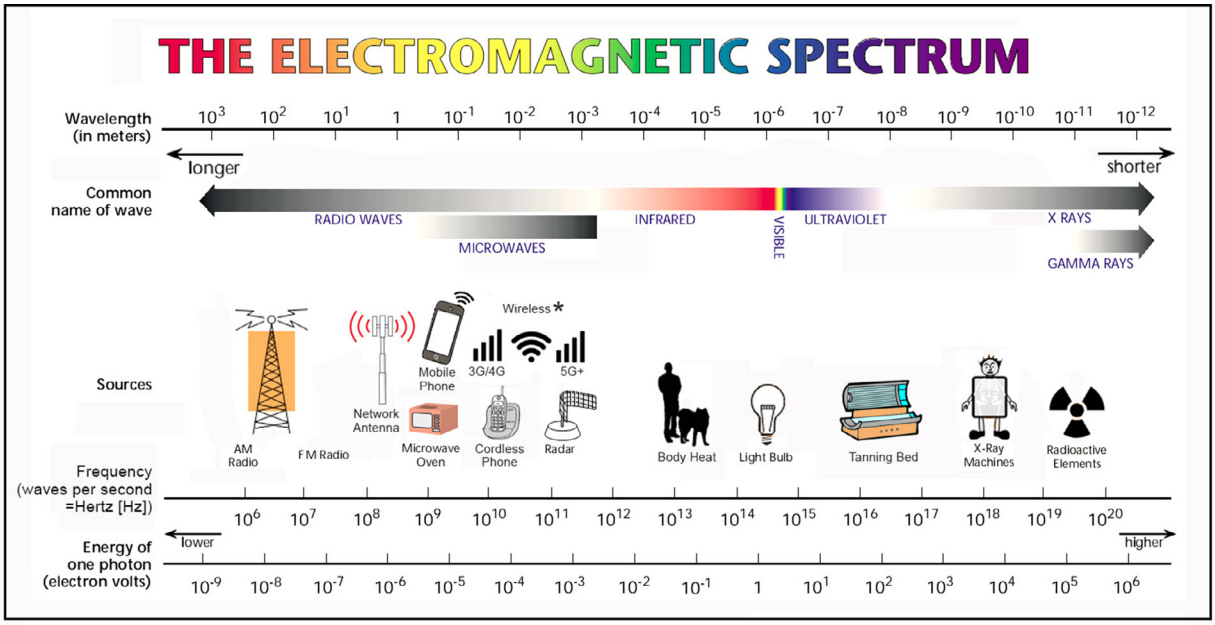

Fig. 4. Electromagnetic Spectrum

* Cellular and cordless phones; computers, laptops, tablets and peripheral equipment; antennae, Wi-Fi, access points and drones; monitors (e.g. security, medical, for babies); toys and entertainment systems; "smart" utility meters and appliances; control systems (e.g. indoor climate or lighting); "wearables"; power transfer/battery charging stations; and more. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

voice or music. This scheme, known as amplitude-modulated (AM) radio, dominated early radio and television broadcasts. However, there is a drawback with such a scheme in that only one operator can use the same radio frequency at a time. For two-way AM communication either, each side must wait for the other to stop and 'release' the frequency (hence the use of 'over' by radio operators) or there must be different carrier frequencies for each channel.

The first generation of cellular phones were little more than AM radio handsets working with 2 channel communication (by using a protocol known as Frequency Division Multiple Access[27] (FDMA) and transmitting to an antenna connected to the telephone network, often using relatively high powers of EMF, up to 5 Watts. Their transmissions could be famously picked up by ham radio operators, as the future King of England discovered to his chagrin, when an intimate conversation between then Prince Charles and his paramour, Mrs. Camilla Parker-Bowles was recorded by a scanner enthusiast.[28] Continuous analogue signals dominated telephone signals via copper wires that knitted together cities and countries, radio and television broadcasts right up until the early 1990s.

To overcome problems of limited exchange, and avoid interference and the embarrassment of royals, digital forms of transmission were introduced. The simplest form of digitization is to modulate a carrier signal, transmitting at a set frequency by multiplying it by zero or one. This is illustrated in Fig. 5.

The first panel in the Figure shows the base sinusoidal signal and is known as the "carrier frequency". The second panel is a digitization that turns on or off the signal. The bottom panel is the result of multiplying the two together, resulting in bursts - pulses- of transmission. A receiver tuned to the carrier frequency will translate the red envelope into ones and zeros, resulting in a digital series and information.

The increase in exposure to electromagnetic radiation

The quantity of data transmitted wirelessly and its associated radiation have increased many orders of magnitude since the inception of TV and radio programming. Rather than weekly anticipation of seeing a star on the Ed Sullivan Show or the next stage of a sitcom, we can now enjoy instant gratification with binge-watching, and endless offerings on many platforms, with important environmental implications,[29] including significantly increased energy and greenhouse gas emissions.

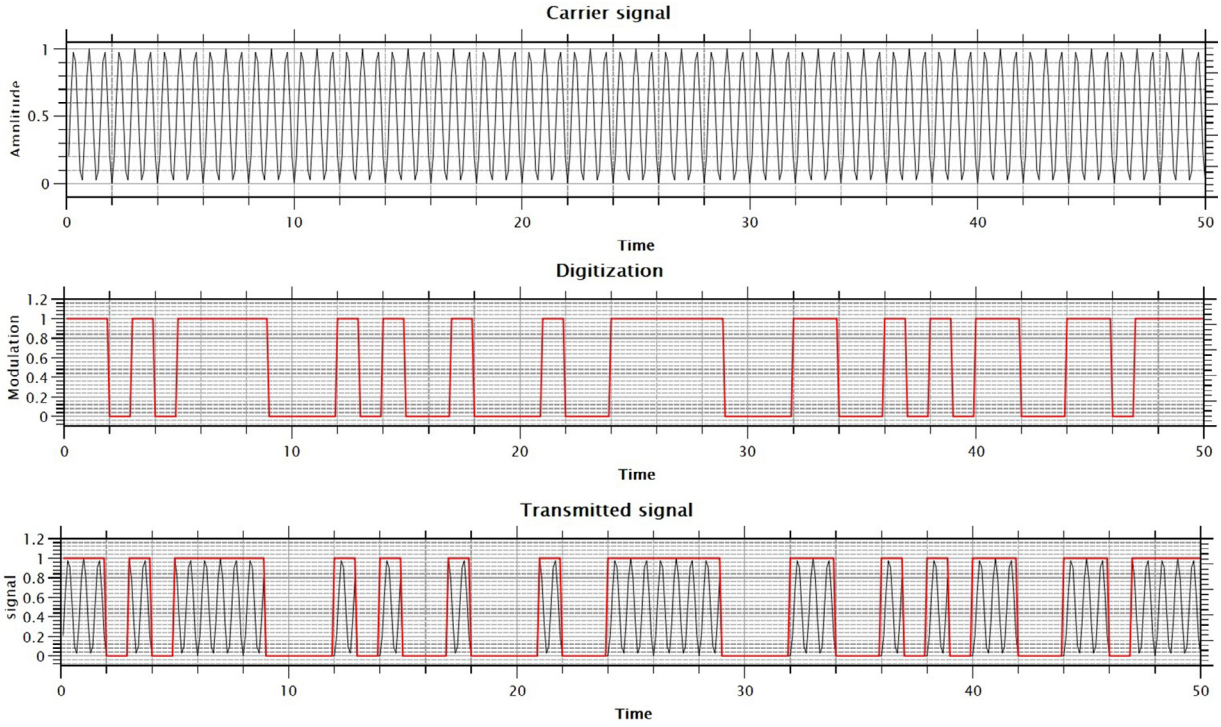

Fig. 5. A simple illustration of how a continuous carrier wave can be transformed into a pulsed signal for digital transmission. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Since the inception of the mobile telephone age (the first commercial cellphone hit the marketplace in 1983[30]) 40 years ago there have been 5 generations of technological advances (see Table 1) culminating in the last 5th Generation (5G) Mobile networks. Each generation has led to consequent increases in exposure to EMR.[31] One often trumpeted claim is that the latest 5G networks will in fact be greener and reduce exposure levels. However, in discussing the energy implications of 5G rollouts, López-Pérez et al. noted in a recent survey that a 5G network may consume over 140% more energy than an equivalent 4G network.[32] Additionally, there is no corroborated evidence that 5G networks will reduce exposures. There are number of studies indicating the opposite will be true[33–36] Some industry experts report that ambient environmental exposures from near antenna installations from 5G and the densification of new wireless infrastructure can exceed those of current 3 and 4G networks up to 46 times.[33,37] 5G networks have multiple beam-forming antennas, located about every 100 m.[32] The public health and environmental impacts of 5G remain untested.

Some industry experts report that ambient environmental exposures near antenna installations from 5G and the densification of new wireless infrastructure can exceed those of current 3 and 4G networks up to 46 times.

Part of the reason for this increase in exposure with 5G is due to the fact that as higher frequencies are used atmospheric absorption and scattering increases. Because 5G frequencies operate along the millimeter wavelengths and signals cannot travel as far as previous systems, they are more prone to disruption from objects that interfere, such as walls and other barriers. Therefore, to maintain the same signal strength more base stations are required, a process known as "densification." Some estimates put the number of additional 5G base stations required for coverage in an urban environment to a 100-fold increase compared to an equivalent 4G network.[34] More base stations translate to more radiation. Another reason that greater exposures can occur is a

TABLE 1. Common cellular technologies and their respective frequency bands in the MHz (106 Hz) and GHz (109 Hz) ranges.[30]

Cellular technology	MHz frequencies	GHz frequencies
GMS (2G)	380 – 900	1.8 – 1.9
CDMA (2G & 3G)	400 – 900	1.8 – 2.5
UMTS (3G)	699 – 900	1.7 – 2.69
LTE (4G)	400 – 900	1.9 – 5.925
5G NR (5G) FR1	600 – 960	1.5 – 6.7
Bluetooth		2.4
Wi-Fi		2.45, 5 and 6
5G NR (5G) FR2	———–	24.25 – 71.0

The acronyms stand for Global System for Mobile communications (GSM), Code Division Multiple Access (CDMA), Universal Mobile Telecommunications System (UMTS), Long Term Evolution (LTE) and 5th Generation New Radio Frequency Range (5G NR FR). **Currently 5G NR FR1 is being nationally deployed, with limited applications of 5G NR FR2 being deployed in some major cities.**

result of the fact that the 5G standard relies on a new technological advance termed Multiple Input Multiple Output (MIMO) antennas. The number of users that can connect to a single base station increases by sharing out the frequency band to many more frequency channels (hence the requirement for higher frequencies) and by dividing the time each individual channel utilizes the same frequency band. In contrast to 2G to 4G standards, this division of frequency bands in 5G is multiplied by using beam-forming antennas. By using many small antennas and by closely timing individual transmissions on the same frequency, it is possible to form the signal into a tightly confined spatial beam from the base station directly to the user's 5G phone, 5G tablet or 5G computer. As long as 2 users are not standing together, they can both use the same signal frequency and not interfere with each other's transmission. These are known as "phased array antennas" and will form the heart of multiple beam-forming antenna and the need for MIMO in the 5G standard.[33] The electromagnetic frequencies utilized for wireless and cellular communications, from 1G up to 5G occupy the Megahertz (MHz) and Gigahertz (GHz) frequency ranges as depicted in Table 1.

How is EMF exposure quantified?

The metric used for measuring personal exposure from cell phones is called SAR (Specific Absorption Rate). It is a gauge of the rate of absorption of electromagnetic energy by the flesh of the user. Properly defined it is the rate of absorption of energy from a cell phone or other wireless device, measured in Watts per Kilogram (W/kg) averaged over a time period of 6 or 30 minutes distributed into a 1 g or 10 g volume within the plastic phantom 12-pound head of a large adult male filled with homogenous fluid or his 220-pound plastic body phantom. A local SAR of 1.6 W/kg is allowed for head and torso, and 4.0 W/kg is permitted for extremities which include the ear (the pinna).

Using a computer-controlled probe that dips into the fluid-filled phantom head (see Fig. 6), the electromagnetic field strength is measured at various points inside the model of 12-pound head of a large adult male. The SAR is then calculated by the equation,

$$SAR = \frac{\sigma \left| E \right|^2}{\rho} \quad (1)$$

where σ is conductivity of the saline solution at the frequency of interest, E is the electric field strength and ρ is the density of the media. The protocol of measurement is dictated by the IEEE standard C95.1-2019.[38] The human phantom is known as the Specific Anthropomorphic Mannequin (SAM) and is standardized by the IEEE.[39] The SAR rating has been criticized as under-estimating absorption for smaller persons and for children by a number of authors[40] because the dimensions of the SAM are based on a model of the 90th percentile of 1989 United States military recruits.[41,42,38] The homogenized saline liquid used to electrically mimic flesh cannot account for the varied and widely differing conductivities and densities of different tissues of different ages.[43] Underlying this model for estimating exposure is the assumption that the only harm that can be caused by an electromagnetic wave is heating of brain or body. In summary, if exposure heating results in a rise in core body temperature of less than 1 °C, then it is considered not hazardous. Criticisms of the SAR are further discussed in Section 7 on the need to update regulatory limits.

A further metric is the Ambient Power Density (PD), measured in Watts per square meter or milliwatts per square centimeter. The ambient PD metric measures the flow of electromagnetic energy per square meter from a distant source, such as a cellphone base station. In the US the safety limit for general public exposure to sources such as base stations, is set at 10 W/m^2 (sometimes quoted equivalently as mW/cm^2).

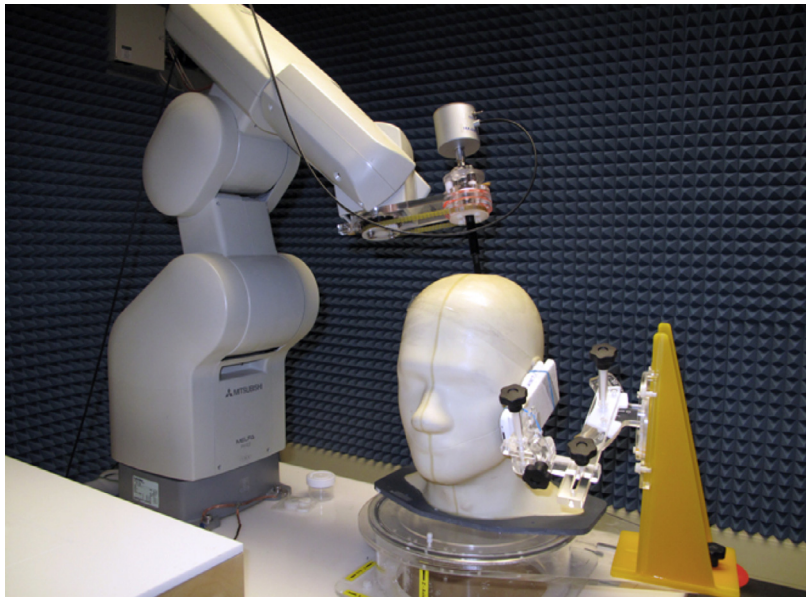

Fig. 6. Cell phone SAR RF test system using Specific Anthropomorphic Mannequin Model.

The origins of the ambient PD and the SAR regulations can be traced to the late 1950s when the U.S. Army and Navy became worried over potential harm to radar operators[44,45] from heating by carrying out studies on a handful of dogs, monkeys and rats. They had noted eye damage and burns from over exposure and the standard for PD was set at 10 W/m.[2,44,46] This became the established paradigm with the issuance of the first American standard in 1966 by the American Standard Association and then by the Institute of Electrical and Electronics Engineers (IEEE) for exposure to RFR and has remained ever since. Further research, including animal behavioral studies when exposed to EMF to a level that did not cause internal heating (of more than 1 ˚C) were used to confirm this initial assumption.[42] In 1996 the US Federal Communications Commission (FCC) set current guidelines for the allowable RFR exposure of the general public to RFR ranging from 300 kHz to 100 GHz (3G up to 5G and above).[47] based on a 1986 Report of the National Council on Radiation Protection & Measurements (NCRP) as well as the Institute of Electrical and Electronics Engineers (IEEE) C95.1-1991 standard.

In 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued its judgment in* Environmental Health Trust et al v. FCC, *finding that the agency had failed to provide a rational record of review of all submitted science and specifically had not shown evidence of examination of studies provided to the agency on the greater vulnerability of children, the impacts of long term exposures, environmental impacts or the failure to update radiation test procedures for cell phones and other wireless devices which have not changed in more than 27 years.

Internationally, many national governments either take their cue for exposure levels from the FCC or from the International Commission for Non-Ionizing Radiation Protection (ICNIRP).[10]

A comparison of the allowed PD limits amongst counties is given in Fig. 7.

ICNIRP grew out of a working committee of the International Commission for Radiation Protection, a non-governmental organization representing professionals and bodies involved in radiation industries.[48]

Numerous publications have criticized ICNIRP as a close-knit invitation-only group that downplays and misrepresents research[49] indicating biological effects at nonthermal levels and

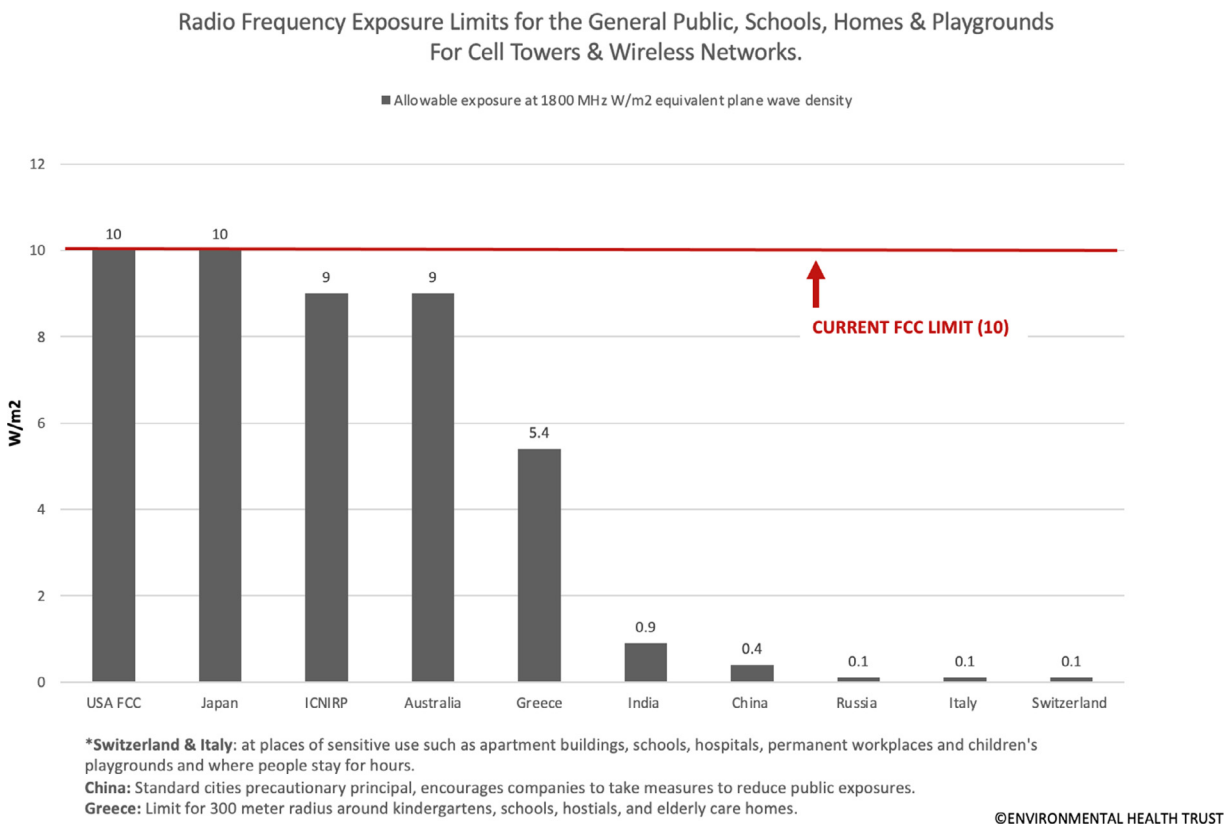

Fig. 7. Country variations for radiofrequency radiation exposure limits.

TABLE 2. ICNIRP and FCC SAR Limits in the U.S. and other countries

SAR Limits for Cell Phones and Wireless Devices	Whole -body average SAR (W/kg)	Head and Trunk * Localized SAR (W/kg)	Limbs and Extremities** Localized SAR (W/kg)	Examples of countries that adapted limits for cell phone and wireless device premarket tests
ICNIRP 100 kHz to 6 GHz All SAR limits averaged over 6 minutes. Local SAR averaged over 10 g of tissue.	0.4 W/kg 0.08 W/kg	Occupational 10 W/kg averaged over 10 grams tissue General Public 2 W/kg averaged over 10 grams tissue cube	20 W/kg averaged over 10 grams tissue 4 W/kg averaged over 10 grams tissue cube	Europe, Mexico, China, Greenland, Canada (for over 6 GHz), most countries in South America except Bolivia, most countries in Africa
ICNIRP (2020) >6-300 GHz *6 minute averaging *ICNIRP states, "Local Sab is to be averaged over a square 4-cm^2 surface area of the body. Above 30 GHz, an additional constraint is imposed, such that exposure averaged over a square 1-cm^2 surface area of the body is restricted to two times that of the 4-cm2 restriction."*	0.4 W/kg 0.08 W/kg	Occupational Local S_{ab} 100 mW/cm^2 General public Local S_{ab} 20 mW/cm^2		Australia
FCC Occupational, averaging time is 6 minutes. General public averaging time ranges from 6 minutes to 30 minutes.	0.4 W/kg 0.08 W/kg	Occupational 8 W/kg averaged over 1 gram of tissue cube General Public 1.6 W/kg averaged over 1 gram tissue cube	20 W/kg averaged over 10 grams tissue cube 4 W/kg averaged over 10 grams tissue cube	United States, India, Panama, Korea, Vietnam, Canada (for under 6 GHz), Iran, Republic of Bolivia, Cuba

ICNIRP's Head and Trunk tissues have both Type 1 and Type 2. ICNIRP defines Type 1 as all tissues in the upper arm, forearm, hand, thigh, leg, foot, pinna (visible portion of the outer ear) and the cornea, anterior chamber and iris of the eye, epidermal, dermal, fat, muscle, and bone tissue. ICNIRP defines Type 2 tissues: all tissues in the head, eye, abdomen, back, thorax, and pelvis, excluding those defined as Type-1 tissue. *Limbs do not contain any Type-2 tissue.

****FCC defines extremities as hands, wrists, feet, ankles, pinna/ ear.**

instead self-references its own commissioners, many of whom have a history of conflicts of interest.[50,51] ICNIRP and FCC limits for SAR are summarized in Table 2.

Despite innumerable studies demonstrating nonthermal biological effects of RFR, discussed below, ICNIRP and IEEE do not recognize non-thermal impacts as sufficiently "established" to be relevant to exposure limits.[7,8,31] Numerous scientific expert groups[7,29,52] such as ICBE-EMF and ORSAA emphatically do not agree with this view. Yet, the FCC reaffirmed their guidelines in 2019, by the expedient of simply reconfirming the existing 1996 standard.[53,54]

In 1996 the US Federal Communications Commission (FCC) set current guidelines for the allowable RFR exposure of the general public to RFR ranging from 300 kHz to 100 GHz (3G up to 5G and above).[47] This led to legal action against the FCC because more than 11,000 pages of published scientific studies and expert recommendations had been submitted to the FCC regarding the need to strengthen its RF exposure guidelines.[55] The FCC failed to provide a rational record of review of submitted science, and specifically did not take into account evidence on the greater vulnerability of children or environmental impacts. Human exposure limits and radiation test procedures for cell phones and other wireless devices have not changed in more than 27 years.

Public exposure limits for radiofrequency radiation from cellphone towers in Italy, Switzerland and Russia are 100 times lower than those of the U.S., last set in 1996.

The World Health Organization (WHO) maintains a dedicated EMF project[56] which collates national government regulations[57] and offers advice to national government agencies. However, the WHO EMF Project has not performed health risk assessment of radiofrequency electromagnetic fields since 1993[58] and several have questioned its independence as well as its role in the global harmonization of EMF standards.[59,60] The World Health Organization International Agency for Research on Cancer (IARC) constitutes a separate entity from the WHO EMF project. IARC classified RFR as a class 2B possible carcinogen in 2011.[61] Within the past few years, the IARC advisory group has recommended a re-evaluation of the body of evidence on cell phone risks to human health, in light of mounting evidence of adverse impacts discussed here.

Public exposure limits for radiofrequency radiation from cellphone towers in Italy, Switzerland and Russia are 100 times lower than those of the U.S., last set in 1996.

Since 1996, measurement of radiation permitted from any particular cell phone is made by testing temperature changes inside a plastic phantom 12-pound head of SAM (Specific Anthropomorphic Mannequin), filled with homogenous saline liquid to mimic the human brain with its diverse tissues and densities, making a 6 to 30 minute phone call, with a spacer between the head and the tested phone to allow for the ear/pinna.

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Physical mechanisms of the interaction of RFR and tissues

New 5G networks are using the frequencies of previous generations, but they can in addition employ higher submillimeter and millimeter wave frequencies. The higher the frequency, the less the radiation penetrates the body, but less penetration does not mean little or no biological impact. To the contrary, UVA and UVB are entirely absorbed in the skin, and can cause important immunological effects throughout the body including on the production of vitamin D. Indeed, immune effects of UV skin exposure can have consequences for the liver, kidney and other major organs, just as do the lower MHz and GHz frequencies that can penetrate deeper into the

body. Importantly, man-made RFR used in wireless and medical devices can be modulated, polarized and pulsed, which greatly influences and can alter their ultimate impacts.[62,63] Electroceuticals constitute an expanding field of clinical applications involving a range of medical devices, from pain control in orthopedics to cancer treatment, biofeedback, and the use of low-strength pulsed electromagnetic fields.[64] As with pharmaceuticals, any agent that promotes healing may also promote illness. It is therefore pertinent to explore potential mechanisms of interaction between tissues and electromagnetic waves.

An important division in the spectrum happens at a frequency of approximately 10^{15} Hz (wavelength 10^{-8} m). While Maxwell's theory, as described above, considers light as classical waves, modern quantum theory embraces a dualism in considering light as both a particle and concurrently as a wave.[65] One can consider an oscillating packet of waves confined spatially and moving as one through space. This is known as a photon and the energy it contains is proportional to the frequency of its oscillation. As the frequency is reduced and wavelengths get macroscopically longer (the wavelength of visible light is measured in hundreds of nanometers, whereas of radio waves in the MHz range the wavelengths are measured in hundreds of meters) the quantum description of light is indistinguishable for the classical theory of Maxwell.

The energy inherent in a photon of light at frequencies of UV and above is enough to cause the ionization of biological molecules. That means that the absorption of the photon by the molecule can result in the breaking of chemical bonds, leading to the destruction of the molecule. Specifically for DNA such an occurrence can lead to the promotion of cancers. At frequencies of radio waves direct ionization of DNA or other molecules cannot happen.

Physical mechanisms of the interaction of RFR and tissues

At the submicroscopic level molecules can be regarded as collections of potentially charged atoms held together by chemical bonds as they share electrons. RFR also affects atoms that tend to be charged; either positively charged "cations" (sodium Na^+ or calcium $Ca^{2+}$for example) or negatively charged "anions" (chloride Cl^-). Consequently, bonds will react to an external electromagnetic field, even if its frequency is not high enough to lead to direct ionization. One can view such a perturbation as gently "nudging" ions. Under certain conditions bonds can change and form new chemicals. Indeed, microwaves are used commercially to speed up and alter products of chemical reactions using "microwave catalysis".[66] Dysfunctional chemical reactions can lie at the root of many distinct forms of ill health for living organisms.

Biological pathways for non-ionizing effects

There are several pathways[67–71] that may be involved in biological effects of RFR, including the induction of ROS leading to oxidative stress, activation of the ERK1/2 signaling pathway, and induction of heat shock proteins. One of the more accepted pathways to damage is the perturbation of Voltage Controlled Calcium Gates (VCCG) by pulsed EMF.[72] VCCGs are an integral part of cell membranes that are responsible for the transport of Calcium ions across the cellular membrane for signaling and regulation of the cellular homeostasis. In 2000 Panagopoulos et al. concluded that the ELF EMF components of wireless communication signals are a critical factor in understanding how exposures can lead to pathology.[72,73] Repeated irregular gating of electro-sensitive ion channels disrupts the cellular electrochemical balance and homeostasis leading to the overproduction of reactive oxygen species. The cascading effects of repeated exposures can lead to numerous biological endpoints including the weakening of cell membranes.

Disturbance in ROS homeostasis leads to a pathological state[74] termed "oxidative stress", which plays an essential roles in regulation of cancer progression. ROS are understood to regulate every step of tumorigenesis and have been found to be upregulated in tumors; this can lead to aberrant signaling. In addition to cancer, oxidative stress plays a role[75] in the development of many other chronic diseases, including diabetes and neurodegenerative syndromes. Reviews of animal and cell studies consistently find even very low non-ionizing EMF exposures are associated with increased oxidative stress. Children whose immune systems are still developing are more vulnerable to these ROS effects.[76,77] In 2019 Lai found strong indications that exposure to static and extremely low frequency electromagnetic fields also affects oxidative status in cell cultures and experimental animals.[67–72]

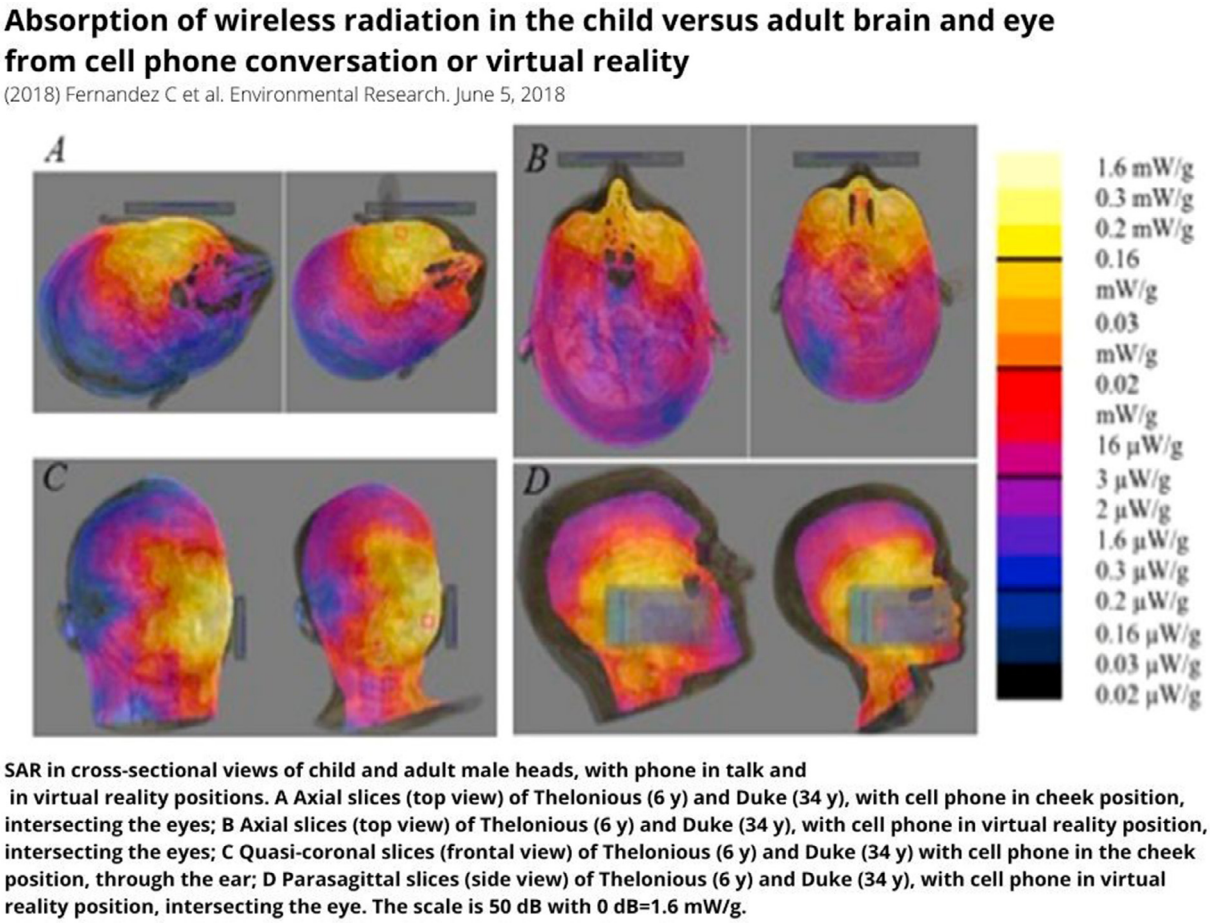

Fig. 8. Absorption of wireless radiation in child vs adult brain and eye from cell phone or Virtual Reality.[70] (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Children's unique vulnerability to wireless radiation

Children are more vulnerable to wireless radiation,[78–81] just as they are to other environmental pollutants[9] and medicines. Present and future generations will have many more hours of cumulative lifetime exposure to RFR, because exposures begin prenatally and continue throughout early and later life.

Children have a unique physiology, that results in proportionately greater RFR absorption compared with adults.[4] Children have smaller heads, resulting in shorter distances for RFR to travel to reach critical brain regions, and their brains contain more fluid that can absorb relatively more energy from radiofrequency radiation sources. Fig. 8[70] shows that simulations of exposure from cell phone use have determined that children absorb up to 10-fold greater RFR in the pediatric cerebellum, 10-fold greater in the bone marrow of the skull and up to 30-fold greater in the hippocampus.[82] Children's eyes can absorb 2 to almost 5-fold higher doses.

Children absorb proportionally more RFR than adults; about 2-fold greater in the pediatric cerebellum, ten-fold greater in the bone marrow of the skull and up to 30-fold greater in the hippocampus. Children's eyes can absorb 2- to almost 5-fold higher doses than adults.

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Children's brain and body tissues have a higher dielectric constant, a measurement of the ease with which electromagnetic fields can move through different media. Peyman[83] documented how the young brain has a higher dielectric constant due to the higher water content and less developed myelin sheath. Bony tissues also change over time depending on the degree of mineralization of the bone matrix. The largest age-dependent variation in dielectric properties is observed in bone because as an animal grows, the high water content of red marrow is transformed to the high fat content of yellow marrow.

Every tissue in the body has unique dielectric properties. For example, the distinctive dielectric properties of normal and cancerous breast are being employed to enhance detection of abnormal cells[84] and to devise EMR-based treatments for the disease.[85]

Pregnancy, infancy and childhood are periods of critical susceptibility, especially for the brain, which is developing rapidly.[86] Children have a faster rate of neuronal cell growth and the fatty protective sheath of myelin is not fully formed until the mid-20s.[87] Even very low levels of an environmental exposure early in development can have lifelong implications for neurodevelopment. Stem cells[88] are more active in children and have been found to be more sensitive to wireless frequencies than differentiated cells.[88]

Cell phones and wireless devices have premarket RF emission tests using the large adult SAM model, with an empty twelve pound head into which homogenous fluid is poured. Devices are not tested using a child's smaller head and body, nor with models of pregnancy.[42] Devices are also tested at a distance from the body, without direct contact between the antenna and the body or skull. This is why most smartphones, Wi-Fi devices and other wireless electronics have instructions, deeply buried in user manuals, which advise that devices be kept at a distance from the body.

Fig. 9[77] shows the radiation pattern simulated from a Wi-Fi tablet into the head of a 6 year old.

Reproduction and pregnancy

Reproductive capacity

Several, but not all reviews[89] of the effects of EMFs on male and female reproductive function have identified numerous serious effects that occur at levels of RFR that do not heat tissues. Gye and Park[90] and Jangid et al.[91] present a number of *in vivo* and *in vitro* experimental studies demonstrating that non-ionizing nonthermal EMF exposure can alter cellular homeostasis, endocrine function, reproductive function, and fetal development. Impacts on both male and female reproductive parameters have been reported, including: male germ cell death, the estrous cycle, reproductive endocrine hormones, reproductive organ weights, sperm motility, early embryonic development, and pregnancy success.

Mechanisms that appear to be involved at the cellular level include increases in free radicals and calcium ions [Ca^{2+}] related to effects of EMFs, which lead to cell growth inhibition, protein misfolding and DNA breaks.

Reproductive parameters reported to be affected by EMF include male germ cell damage and death. Females may experience impacts on the estrous cycle affecting ovarian follicles, reproductive endocrine hormones and reproductive organ weights. Effects on reproduction include impairments of early embryonic development, fertilization, miscarriage and a variety of pregnancy-related outcomes. As with other endpoints, experimental effects on reproductive function differ according to frequency, polarity, wave-form, strength (energy), and duration of exposure.

A robust body of research on the male reproductive system specifically has found decreased testosterone[92] as well as impacts to sperm viability,[93] motility and morphology[68,94–100] from current levels of RFR resulting from use of cell phones or other devices.

The induction of oxidative stress[101] is understood to be a key pathway of action that underlies the biological impacts of RFR on the reproductive organs and also can play a major role in the induction of cancer as discussed below.[101] At the cellular level, increased free radicals impact mitochondrial metabolism and affect nitric oxide levels and antioxidant mechanisms.[102] RFR may alter membrane transport and integrity, affecting ion (e.g., calcium) transport; these are among mediators of effects of EMFs that lead to cell growth inhibition, protein misfolding and DNA breaks. See Fig. 10.[56,92]

Acute exposure can stimulate plasma membrane NADH oxidase and increase the production of ROS. Increases in ROS can stimulate endothelial growth factor (EGF) receptors which in turn activate extracellular signal regulated kinase (ERK) pathways. The ERK pathway consists of subsequent activation of

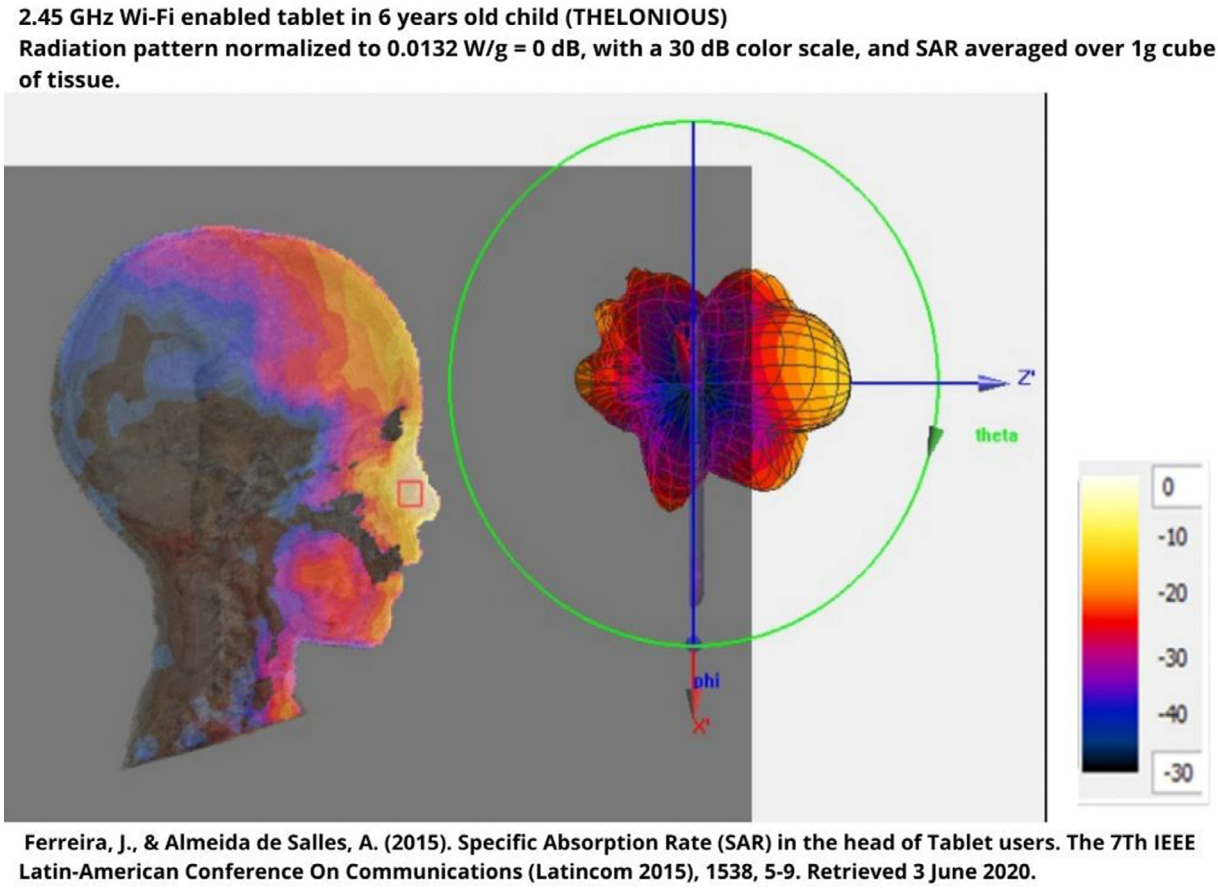

Fig. 9. Radiation pattern from 2.45 Wi-Fi enabled tablet into model of 6-year-old head. Radiation pattern normalized to 0.0132 W/g = 0 dB, with a 30 dB color scale, and SAR averaged over 1g cube of tissue.

Ras, Raf proteins, and mitogen-activated protein kinase (MAPK). The MAPK pathway also has a tumor promoting role. Chronic exposure to ROS can activate various stress kinases (p38 MAP kinase), stimulate the ERK pathway, and also lead to phosphorylation of heat shock proteins (Hsp) that inhibit apoptosis, thereby promoting survival of damaged cells and carcinogenesis. Hsp can increase the permeability of the blood-testis barrier and produce infertility. RFR also can interfere with membrane calcium channels and promote cancer by stimulating ornithine decarboxylase, a rate-limiting enzyme in polyamine synthesis.

Pregnancy is a critical window of vulnerability

In both animals and humans, prenatal EMF exposures have been linked with impaired development of structures and functions of the brain, as well as the reproductive organs and reproductive capacity of offspring. Experimental and epidemiological evidence indicates that prenatal impacts could range from impaired oogenesis and spermatogenesis, to reduced volume and number of brain pyramidal cells, other serious neuronal impairments, ovarian dysfunction[103] as well as increased DNA damage in multiple organs[104] of offspring.

Damage to oocytes in female offspring can in turn affect fertility as well as the health of following generations. Daily exposure of young Sprague-Dawley female rats for 2 h of GSM radiation for 1 and 2 months produced inflammation and impairment of ovarian function[103] consistent with endometritis, a growing problem for young adolescents. Intergenerational impacts are increasingly being understood; a 2021 study of more than 200 mother-daughter-granddaughter triads, found that granddaughters of those who had been in the top third of DDT exposure during pregnancy had 2.6 times the chances of having an unhealthy body mass index by their mid-twenties and

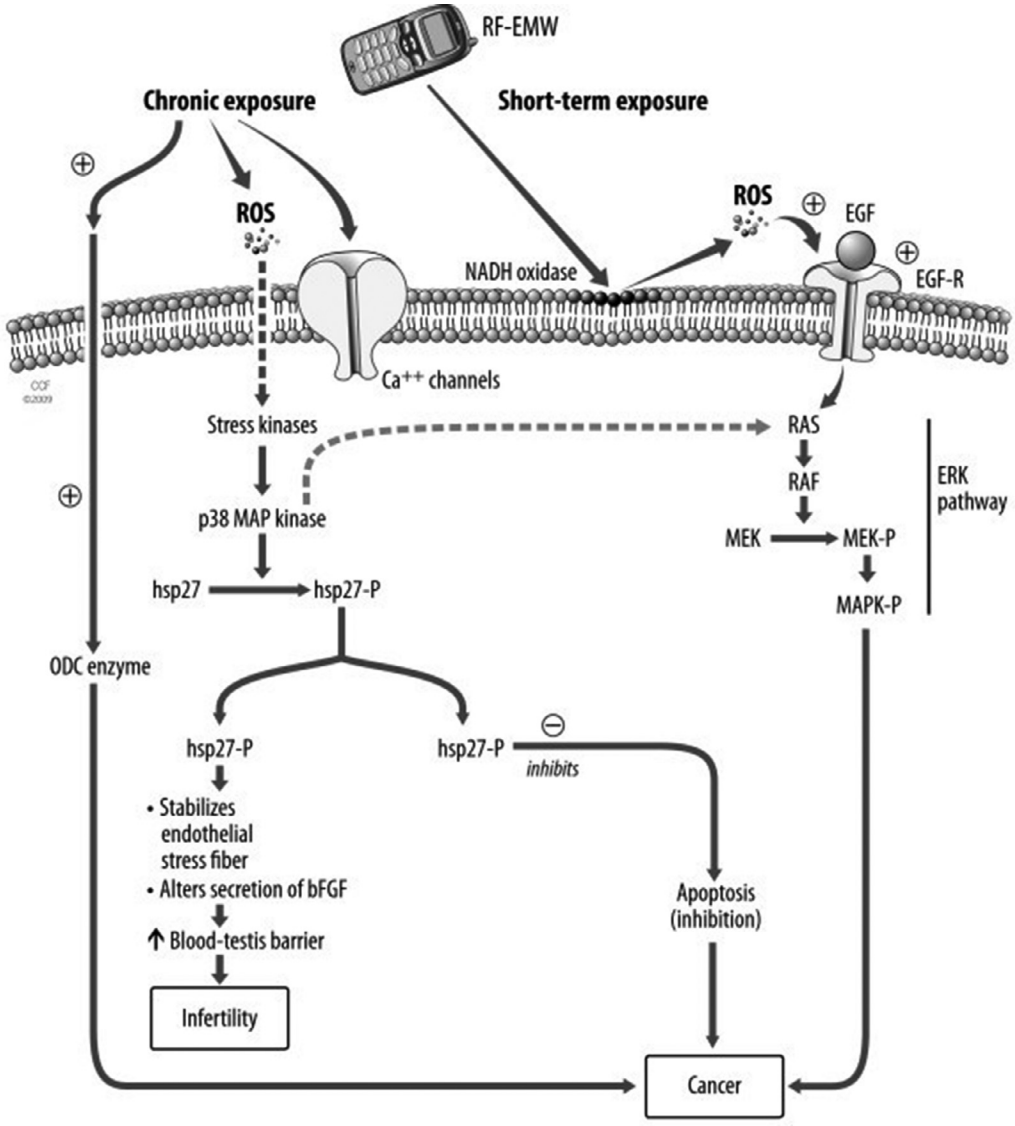

Fig. 10. Acute and chronic impacts of cell phone radiation on male reproduction. The Figure shows various acute and chronic cellular targets of radiofrequency electromagnetic waves (RF-EMW).[56,92]

were more than twice as likely to have started their periods before age 11—both of which increase their chances of developing breast cancer and other chronic illnesses later in life.[105]

Toxicological evidence of adverse impacts of RFR

Experimental studies form the foundation for evaluating pharmaceutical agents and other chemical and physical environmental exposures that can affect pediatric health. *In vitro* studies of well-established animal cell lines and human cell lines constitute one effective source of information that can be used to predict and prevent harm in humans. Employing validated rodent and other models, both short term and long-term *in vivo* studies on rodents and other animals are employed to clarify physiological consequences of exposures.

Studies of prenatal impacts can yield information on birthweight along with longer term consequences for health of offspring into adulthood. While the key male role ends at fertilization, damage to sperm *in utero* may have transgenerational effects on offspring.[106] There is growing evidence that male-mediated factors

relating both to preconception and fertilization, as well as prefertilization and perifertilization exposures also play roles in determining health outcomes of progeny. In addition, early-life RFR exposures have been demonstrated to cause a range of negative impacts on male and female reproductive health, including damage to the testicular proteome[107] and low birthweight. After a month of 4 h daily controlled exposure to nonthermal levels of cell phone radiation, signaling proteins in the rat testes and sperm production were significantly altered, indicating impaired reproductive function and increased cancer risk.

Experimental studies are especially useful in understanding the roles of avoidable early-life environmental exposures on outcomes that affect children and adolescents, since controlled human studies are unethical. As a result, most human studies that can be used to clarify the impact of RFR are observational. Frequently, such studies are opportunistic, complex and expensive, and also challenging to interpret with poor quality longitudinal data, and limited exposure data, particularly with evolving uses of ever-changing technologies. In the real world, children are exposed to numerous sources of RFR at various frequencies and modulations throughout their daily lives. Smart phones can operate with 5 or more antennae simultaneously sending and receiving radiation to and from towers or routers, as most apps are set to update automatically. Yet, most experimental studies only look at a single frequency at a time.

Prenatal exposures and the central nervous system

Over the past two decades a number of experimental investigations have found that prenatal exposure to some EMF negatively affects both the structure and function of the adult central nervous system (CNS).[108–110] As an example, a series of experiments by Odaci, Bas and Kaplan and colleagues measuring impacts through stereological analysis demonstrated that rodents exposed prenatally to 900 MHz had fewer cells and more indications of damage in various brain regions of the hippocampus responsible for learning and memory.[111] Likewise, studies on postnatal exposures of 8 week old rats also found impacts on hippocampal pyramidal cells.[112,113] This team also found prenatal and postnatal impacts occurred to the Purkinje cells in the cerebellum. The cerebellum is critical to memory, balance and impulse control and appears especially vulnerable to RFR. Others have hypothesized that RFR might also alter the membrane current of Purkinje cells within the cerebellum. Haghani et al. evaluated properties of Purkinje cells[108] following prenatal exposure to 900 MHz EMF and found that exposed progeny had significantly reduced spontaneous cell firing. While these areas of the brain have been well characterized after prenatal EMF exposure, it is likely that many other areas of the brain are similarly affected.

Prenatal exposures in humans alter behavior and cognition in offspring

Although they are few in number, human studies investigating *in utero* exposure to wireless and other non-ionizing EMF have found a variety of adverse effects on pregnancy outcomes as well as the health of offspring regularly exposed to EMF or EMF/RF.

Several studies by a team from Kaiser Permanente lead by Dr. De Kun Li report a range of impacts to pregnancy and offspring. They measured pregnant women's exposure to magnetic fields (MF) early in pregnancy using an EMDEX Lite meter (Enertech Consultants Inc.) that measures magnetic field MF exposure for 24 h during a typical day, and providing a detailed diary of activities to allow the researchers to: (1) identify locations of daily activities (at home, at home in bed, in transit, at work, and other); (2) verify if activities were reflective of a typical day; and (3) examine if locations and activities were associated with high MF exposure. Women and their progeny were followed over several years. After controlling for multiple other factors, they found that women who were exposed to higher MF levels had 2.7 times the risk of miscarriage compared to those with lower MF exposure, a finding that corroborated earlier research by the same team.[114] Later publications also found higher *in utero* MF exposures associated with childhood obesity, asthma, and ADHD.[115–117] Similarly designed research[118] that measured MF exposure with the EMDEX meter found lower neural volume and bud length, measured by ultrasound, in embryos of women with higher workplace and other exposures to EMF, who were seeking induced abortion of unwanted pregnancies that were terminated in the first trimester. Women in the top quartile of MF exposure had a four-fold increased risk of a shorter embryonic bud length than those in the bottom quartile.

Greater habitual self-reported maternal mobile device use was associated with less infant recovery upon reunion.[119]

Behavior and cognition in children and adolescents affected by cell phones

Researchers at the University of California School of Public Health in Los Angeles published studies in 2008 (13,159 children)[120] and 2012 (28,745 children)[121] that found that exposure to cell phones prenatally—and, to a lesser degree, postnatally—was associated with behavioral difficulties such as emotional and hyperactivity problems at the age of school entry. Although smaller studies have not found an association, in 2017 the largest study to date of 83,884 mother-child pairs in the five cohorts reported that high prenatal cell phone use was linked to hyperactivity/inattention problems in children, while no prenatal cell phone use was linked to low risk for any behavioral problems. The association was fairly consistent across and between these large cohorts. The nearly 40% of the cohort[122] reporting no cell phone use during pregnancy were much less likely to have a child with overall behavioral or emotional problems, while those with the highest reported use during pregnancy had 1.5 times more such problems documented in their children. The authors indicate that the "interpretation of these results is unclear as uncontrolled confounding may influence both maternal cell phone use and child behavioral problems." Greater habitual self-reported maternal mobile device use was associated with less infant recovery upon reunion.[119]

In addition, two studies reported consistent evidence associating RFR with lower figural memory performance in adolescents. Foerster et al.[123] confirmed Schoeni et al[124] in a larger study population of 843 adolescents. Teens who used the phone against one side of their head scored more poorly on tests that measured memory skills specific to the most highly exposed brain regions

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Behavior in animals

In addition to effects on brain development, pre- and post natal EMF exposures in numerous studies have found that cell phone radiation significantly affects a range of learning, memory, and behavior disorders in rodents.[125–136] Thus, Aldad et al. showed that prenatal exposures to conventional cell phone radiation throughout pregnancy resulted in impaired memory and hyperactive behavior, as well as altered neuronal developmental programming, glutamatergic-synaptic transmission onto pyramidal neurons of the prefrontal cortex. Fragoupoulou and Margaritis demonstrated in several studies that animals exposed to radiation have impaired performance on several standard measures of learning. Employing the standard Morris water maze test of hippocampal-dependent spatial memory, they showed that just 2 h per day of exposure to pulsed nonthermal cell phone signals of 900 MHz resulted in significant deficits in performance in exposed animals. Moreover, sham-exposed animals showed the expected preference for the target quadrant, while exposed animals showed no preference. These results indicated that the RFR exposed mice had deficits in their capacity to consolidate and/or retrieve and recall learned spatial information.

Despite these and numerous other studies demonstrating nonthermal impacts of RFR, standard setting groups such as IEEE and ICNIRP generally dismiss experiments that use actual transmitting devices (cell phones, Wi-Fi routers) in their studies, arguing that the exact exposures are not adequately quantified. Indeed, it is true that real devices emit constantly varying signals and erratic pulsation patterns that are more bioactive than can be produced through controlled laboratory simulations.[137] A number of other expert groups including the ICBE-EMF and ORSAA contend that employing actual phones and devices in controlled studies with shielded systems can yield important findings that are more realistic than those achieved through other means. In fact, experimental

studies employing real mobile phone exposures are fairly consistent in showing adverse effects.[138] As an example, Aldad and colleagues[139] provided evidence that prenatal exposures to RFR from an operating phone significantly alter behavior of offspring.

Mice prenatally exposed to cell phone radiation from operating phones (800-1900 Mhz) through gestation exhibited behavioral and neurophysiological alterations that persisted into adulthood.

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The prenatally exposed mice were more hyperactive, with diminished memory and decreased anxiety. Findings further demonstrated impairment of glutamatergic synaptic transmission among pyramidal cells in the prefrontal cortex associated with these behavioral changes, suggesting a mechanism by which these exposures could lead to increased prevalence of neurobehavioral disorders. There was a significant trend across the groups treated for 0, 9, 15, and 24 h/day demonstrating that evidence of damage increased in direct proportion to the amount of exposure the animals experienced. Mice prenatally exposed to cell phone radiation from operating phones (800-1900 Mhz) through gestation exhibited behavioral and neurophysiological alterations that persisted into adulthood.

Mice exposed to mobile phone radiation at levels well below the permissible ICNIRP exposure limits for human-head exposure (SAR 2 W/kg) induced hippocampal lipidome and transcriptome changes that may underlie brain proteome changes and memory deficits.

In another example, Broom exposed mice to non-thermal levels of long-term evolution wireless (LTE) 1846 MHz downlink from late pregnancy (gestation day 13.5) to weaning (postnatal day 21) and observed 28-day-old offspring. They found significant effects on both eating behaviors and activity, and concluded that repeated exposure to low-level RFR in early life may have persistent and long-term effects on adult behavior.[140]

After finding cell phone radiation exposure affected spatial memory in mice, researchers from the Department of Cell Biology and Biophysics at the University of Athens, Greece conducted experiments investigating brain proteome responses in mice following whole body exposures to mobile phone or wireless DECT base radiation.[141] They found that long-term irradiation from both sources significantly altered the expression of 143 proteins in total, in critical brain regions such as the hippocampus, cerebellum, and frontal lobe. They speculated that these "underexpressed" or "overexpressed" proteins following EMF exposures may play a role in short term or long-term effects of RFR reported in humans as a consequence of mobile phone exposure, including memory deficits, headaches, sleep disorders, and brain tumors.

Mice exposed to mobile phone radiation at levels well below the permissible ICNIRP exposure limits for human-head exposure (SAR 2 W/kg) induced hippocampal lipidome and transcriptome changes that may underlie brain proteome changes and memory deficits.

Thus, Fragopoulou et al. showed that phone radiation (SAR 0.022−0.366 W/kg), well below ICNIRP limits for human-head exposure but comparable to SAR levels produced in human brain regions induces substantial phospholipid fatty acid remodeling in the brain, on the one hand, and on the other hand, alters the expression of genes that are implicated in lipid metabolism. These mechanisms are hypothesized to account for the deficits in memory that this group has reported.[142] Mice exposed to mobile phone radiation at levels well below the permissible ICNIRP exposure limits for human-head exposure induced hippocampal lipidome and transcriptome changes that may underlie brain proteome changes and memory deficits.

Carcinogenicity

In 2011 WHO/IARC designated wireless RFR as a Class 2B "possible" carcinogen based largely on

studies of heavy cell phone users, that found increased risks for tumorsboth glioblastoma brain tumors and acoustic neuroma, as well as some experimental data with animals. Earlier, in 2002, magnetic field ELF-EMF was also classified Group 2B possible carcinogen due to studies associating residential magnetic field exposure with childhood leukemia.[143] This association continues to be observed.[144,145]

Since the 2011 WHO/IARC designation, several large animal[71,146–148] and case-control human[149–152] studies investigating carcinogenicity have been published associating RFR with cancer. A 2020 systematic review and meta-analysis[153] of case-control studies found that 1,000 or more hours of cell phone use, or about 17 min per day over 10 years, was associated with a statistically significant increase in tumor risk.

Experimental carcinogenicity evidence

Every agent proven to cause cancer in humans will also produce it in animals when adequately tested—World Health Organization, International Agency for Research on Cancer

The international gold standard for rodent carcinogenicity studies has been developed by the U.S. National Toxicology Program (NTP), a program supported by several major federal agencies (NIH, CDC, FDA) that carries out transparent studies. To date the NTP has evaluated more than 600 different physical and chemical agents for their potential to cause cancer in animals under carefully controlled conditions. Every agent proven to cause cancer in humans will also produce it in animals when adequately tested—World Health Organization, International Agency for Research on Cancer.

In 2018, the NTP released the results of their large-scale rodent studies on cell phone radiation, which used non-thermal levels of RFR designed to mimic cell phone exposures. Especially relevant for pediatrics and long-term human impacts is the finding that the rodents exposed prenatally to RFR had significantly lower birth weights compared to unexposed animals. This finding constitutes an important signal that nonthermal radiation levels can impair development, as low birth weight is understood to reflect an important lifelong risk factor for adult health.

The NTP found significant increases in relatively rare and highly malignant schwannomas of the heart and gliomas in male rats. These tumor types are the same histotype found to be increased in epidemiological studies of long-term cell phone users.

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The NTP study also reported increases in DNA damage[71] in both mice and rats and the induction of cardiomyopathy of the right ventricle in male and female rats.[147,148]

When it was completed in 2018, the NTP study, which followed long-established protocols, was the largest rodent bioassay ever conducted on cell phone radiation that began with prenatal exposures and ended after 24 months of exposures. Soon afterwards, the Ramazzini Institute[146] employing similarly controlled protocols released its findings from an even larger animal study of 2448 rats, which employed both similar and lower exposures comparable to those of base stations such as Wi-Fi, and observed the same types of malignant tumors—schwannomas of the heart—in male rats. Overall, these two large scale animal studies alongside the human data[153] provide reasonably strong evidence of the potential for non-thermal levels of RFR to cause cancer in humans.

Every agent proven to cause cancer in humans will also produce it in animals when adequately tested—World Health Organization, International Agency for Research on Cancer

Analysis of the NTP and Ramazzini data according to current risk assessment guidelines concluded that to be consistent with other toxicological assessments, the protection of children requires that U.S. government

FCC limits should be strengthened by 200 to 400 times.[154]

U.S. RFR exposure standards would lower current standards by 200 to 400 times, if they were consistent with usual methods for assessing risks for chemical and other hazards.

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Cancer epidemiology—Case-control studies

The multi-nation Interphone case-control study[155] from 2010, defined a cell phone user as someone who made one call a week for 6 months. That study did not include any cases from the U.S., was led by the IARC, and reported no overall increased risk of brain cancer with cell phone use, but did find that the highest users of phones incurred the greatest risk. Combining participants with little phone use with those with heaviest use diluted the chances of finding any effect.

The case-control MobiKids study of 352 brain cancer patients between the ages of 10 to 24 reported cell phone use; it also found no overall increased risk for brain tumors in the age group diagnosed between 2010 and 2015. The latency for brain cancer in adults is known to range up to four decades; in children it is believed to be shorter. In fact, only 5% of the study participants—17 individuals—had used cell phones for more than 5 years. Unsurprisingly, no evidence of significant association emerged. This study has also been criticized as methodologically flawed[156] especially as so few of the participants had significant exposures to cell phones. Although no overall increased risk was reported for brain tumors in the temporal region of these young cases an increased risk was found in the age groups 10–14 and 20–24 years–age groups that had lived long enough to have incurred more exposure than the younger children included in this study.

Researchers examining the Canadian MobiKids cohort carried out sophisticated statistical modeling including potential sources of biases and probabilistic methods, and did not find strong evidence of an association between reported cell-phone use and meningioma, acoustic neuroma, or parotid gland tumors—tumors plausibly linked with cell phone radiation, but they did note a significant association with glioma.

For glioma, when comparing those in the highest quartile of use (>558 lifetime hours) to those who were not regular users, the odds ratio among Canadian children participating in Mobikids was 2.0 (95% confidence interval: 1.2, 3.4). After adjustment for selection and recall biases, the odds ratio was 2.2 (95% confidence interval: 1.3, 4.1).

Despite major limitations in design, the Mobikids study of cell phone use in Canadian children reported a doubled risk of glioblastoma multiforme from using cell phones, a risk that should provide a sobering message to those that seek to prevent such disease from occurring in the first place.

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More recent case-control studies of glioma in adults from Sweden[157] and France,[149] and systematic analyses that combine data on adult cell phone users carried out in China find 10 years or more of cell phone use significantly associated with increased risk of glioblastoma, with 20 years of exposure resulting in a more than doubled risk. Analyses of shorter-term exposures, such as predominated in the Interphone study, do not find such an association, suggesting that there is a latency of 10 years or more for glioblastoma. Thus, in those few studies that have followed longer term users, more hours of use and longer time periods of use have been found significantly associated with between a 40% to more than 200% increased risk of glioblastoma.

Cancer epidemiology—Cohort studies

In contrast to case controls studies, the UK 'Million' Woman Cohort study and the Danish Cohort Study constitute two studies often cited as proof that there is no relationship between cell phone use and brain cancer. Both have been roundly criticized for serious shortcomings. For example, in the UK cohort study of almost 800,000 older menopausal women, only 18% of cell phone users[158] talked 30 or more minutes per week, as self-reported from 2001 to 2011. Yet, the U. K. study combined slight and regular mobile phone users into a single category and compared them with those who reported no phone use. More than 80% of UK households had landlines during the study period. It is likely many in this cohort also used cordless phones, yet, this significant additional source of RF was not evaluated. In fact, the UK cohort authors acknowledge[159] their study was unable to assess the risks associated with considerably greater levels of exposure. Consequently, the authors note that: "advising heavy users on how to reduce unnecessary exposures remains a good precautionary approach."

Other cancers plausibly reported in epidemiological studies to be tied with cell phone radiation include: thyroid cancer, early-onset breast cancer, early-onset colorectal cancer, and testicular cancer. In a certain subset of those with a common genetic susceptibility, heavy cell phone usage is associated with significantly doubled risk of thyroid cancer.[69] Since the advent of smart phones in 2010, phone antennas tend to be located at the bottom of phones As a result, peak phone RFR exposure is more likely to occur in the neck than in the brain.[160] Smart phones include several different antennas, each one of which can send and receive RFR, with multiple antennas for data, photos, video and other applications located around the phone perimeter. In addition, women who have carried phones in their bras or worn Vocera devices next to their chest have developed unusual patterns of breast cancer, with tumors sometimes appearing precisely under the areas where their phone antennas were located.[161,162]

In those few studies that have followed longer term users, more hours of use and longer time periods of use have been found significantly associated with between a 40% to more than 200% increased risk of glioblastoma.

Several independent analyses published since the original IARC assessment in 2011 conclude that if the criteria that the WHO/IARC relied on when determining carcinogenicity were applied to current science, this would result in classification of cell phone radiation as a probable carcinogen (Group 2A) or proven (Group 1) human carcinogen.[7,8,16,163–167]

Unexplained increases in pediatric and young adult cancers are consistent with increasing wireless exposures

Trends in cancer can provide signals about underlying etiologic factors, as occurred with increases in lung cancer in male and female smokers in the mid-twentieth century, and increases in the rare clear-cell adenocarcinoma of the cervix in young women whose mothers had used diethylstilbestrol to prevent miscarriage.[168] Cancers tend to have multiple contributory causes, which can ebb and flow over time. Over the last several decades, incidence of several different early-onset cancers in adults[169] below 50 years of age have increased in many nations, including those of the breast, colorectum, bone marrow, and thyroid. Although explanations for these patterns will certainly be multi-factorial, wireless radiation is one of the factors that should be more widely explored.

Rates of rectal cancer have quadrupled in those under age 24 in the past decade in the U.S. and Iran and risen rapidly[170] in the U.K, Egypt, and Brazil. One recent study[171] asserts that these increases could, in part, be associated with radical changes in exposures to cell phone radiation due to devices kept close to the body for extended periods of time. More and more children and young adults keep transmitting smartphones with their multiple antennas that are constantly updating apps next to their abdomens inside their tight clothing for hours a day, along with a wireless earpiece in their ear. Thus, although speaking directly into phones has declined, close proximity to their radiation has not.

What makes the potential connection between colorectal cancer increases and cell phone exposures

especially plausible is an experimental study showing that colon and rectal cells are exquisitely sensitive to non-ionizing radiation like that emitted by phones today. Moreover, exposure to non-ionizing mobile phone radiation can lead to effects on treated colon tissues of rats similar to those observed from ionizing 3Gy gamma radiation. Mokarram et al.[172] reported that epigenetic patterns of the estrogen receptor (ERα) after exposure to ionizing radiation paralleled those occurring after exposure to non-ionizing RFR. Using biomarkers that have previously been established to signal damaging exposures, they further found that methylation patterns may constitute an important validated biomarker of exposure to radiofrequency radiation that has the potential to play a role in the expression and promotion of colorectal cancer.[172]

EMFs as endocrine disruptors

Endocrine disruptors are understood to be agents, either natural or man-made, which can mimic or interfere with the body's hormones and disrupt development leading to a range of developmental, reproductive, neurological, and immune problems, as well as cancers. Common sources include plastics, metal can liners, detergents, flame retardants, and pesticides.

EMF exposures have been linked to a range of classical endocrine disrupting effects.

A team from the California Institute of Behavioral Neurosciences & Psychology reviewed the effects[173] of both RFR and ELF on thyroid gland hormones and histopathology and found evidence that RFR was associated with alterations in T3, T4, and TSH hormone levels, disruption of the function of the HPG axis leading to thyroid insufficiency and hyper-stimulation of thyroid gland follicles. This caused apoptosis of follicular cells. Non-ionizing radiation was seen to be significantly associated with histopathological changes in the thyroid gland follicles and the authors contend that non-ionizing EMF radiation might be responsible for the recent increase in the incidence of thyroid insufficiency and cancer in the general population.

Critical research needs to be conducted to understand the effects especially to future generations. Cantürk et al.[174] investigated the effects of pre- and postnatal 2450 MHz RFR on the thymus of rats over four generations and found that the number of pups and weight of all rats decreased significantly in the third-generation.

RFR has all the classic hallmarks of endocrine disruptors that affect reproduction, development of the hypothalamic-pituitary-gonadal axis (HPG) and alter normal male and female reproductive endpoints.

Thus, it appears that non-ionizing [175] RFR has all the classic hallmarks of endocrine disruptors that affect reproduction, development of the hypothalamic-pituitary-gonadal axis (HPG) and alter normal male and female reproductive endpoints. Alterations in spermatogenesis and oogenesis, for example, in turn affect a number of endocrinological and other functions throughout life, including fertility and behavior in offspring along with the risk of cancer, neurological disorders and other chronic illnesses.

Animal studies of additive or synergistic effects of RFR with other agents

Replicated experiments show that RFR can have important co-carcinogenic and tumor promoting effects when combined with known carcinogens. Lerchl et al.[152] found carcinogen-induced tumor rates were significantly higher in mice exposed to nonthermal doses of radiofrequency below current regulatory limits. The authors argued that it was a "very clear indication that in principle tumor-promoting effects of life-long RFR exposure may occur at levels supposedly too low to cause thermal effects."

The Ramazzini Institute performed two large lifespan rat cancer studies[176] combining magnetic field non-ionizing EMF with either acute exposure to gamma radiation or chronic exposure to formaldehyde in drinking water and found significantly greater incidence of malignant tumors with either co-exposure than occurs without such combined exposures.

Investigators from the Beijing Institute of Radiation Medicine in China have also produced important evidence of synergistic effects. They determined that combining 2.8 GHz and 1.5 GHz microwaves[177] impaired spatial memory much more strongly than exposures to a single frequency. It is important to realize that such combined frequencies can easily occur at this time within a single smart phone that can operate on different frequencies at the same time. This same team has reported[178] that exposure to nonthermal levels of 2.8 GHz and 9.3 GHz—as could occur with 5G networks— led to significant impacts to the thymus and spleen, such as congestion and nuclear fragmentation of the lymphocytes, and more severe injuries. Their transcriptomic and proteomic analysis of peripheral blood and spleen suggested that alterations of DNA replication, cellular metabolism, and signal transduction might be involved in microwave-induced immune activation. The spleen not only filters blood-borne pathogens and antigens but also plays a critical role in immune system regulation.

Higher levels of adolescent screentime,[179] social media access[180] and cell phone use in teenagers' bedrooms are associated with reduced sleep time[181] as well as negative effects on daily functioning,[180] behavior[182] and mood.

Effects of screen time

Higher levels of adolescent screentime,[179] social media access[180] and cell phone use in teenagers' bedrooms are associated with reduced sleep time[181] as well as negative effects on daily functioning,[180] behavior[182] and mood. An ever growing body of evidence[183] is associating[184] children's addictive and excessive use of screens and digital media with a myriad of adverse social (relationships, social skills, cyberbullying), psychological (anxiety, depression, suicidal ideation, obsessive compulsive disorder[185]) neurodevelopmental (cognitive development, behavior, attention, speech[186]) and physical (obesity, high blood pressure) consequences. Key factors[187] determining screen time effects include duration, content, media type, degree of access to social media, whether screens are located in the bedroom[180] and the amount of after dark/evening use.[180,187]

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Axelsson et al.[188] found the amount of time spent with screens predicted shorter sleep in preschoolers. Regardless of the time of day that screens were accessed by children, greater screen time was associated with poorer sleep quality, poor communication, poor problem solving and greater attention problems. The AAP notes,[184] "the prevalence of problematic Internet use among children and adolescents is between 4% and 8%.

Up to 8.5% of U.S. youth 8 to 18 years of age and 4.6 % of Chinese youth meet criteria for Internet gaming disorder defined by the World Health Organization in its standard Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) as an uncontrollable, persisting need to engage directly with digital media and games that cannot be stopped.

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This diagnostic code is included in the DSM-5,[189] and in the 11th Revision of the International Classification of Diseases (ICD-11[6]), signaling interference with socialization, including disturbing important areas of life such as family relationships, school, work, eating, bathroom habits and sleep. In its criteria for gaming disorder, the WHO does not include in its criteria any specific number of hours spent with screens, but instead focuses on the inability to engage in normal social life of young children and teens, including outdoor activities as well as socializing indoors with family and at school. The category of internet gaming disorder was added in 2019. According to Pew,[190] 97% of teen boys and 83% of girls play games on

some kind of device. How many of them are addicted is a matter that should be seriously examined, as the toll on pediatric mental and physical health continues to mount.

Higher screen time has been associated with a higher prevalence of prospective disruptive behavior disorders.[191] Clinicians[187,192] posit that the effects of electronic screen time can mimic or exacerbate psychiatric disorders as the interactive media can lead to chronically high arousal levels which can lead to nervous system dysregulation. As a consequence, treating physicians have developed treatments including an "electronic fast" to rebalance the brain and relieve overstimulated reward (addiction) and sensory pathways. Interventions such as reducing screen media have been found to result in a substantial increase in children's engagement in physical activity[193] and increasing outdoor "green" time[194] is beneficial to mental health as well as lowering myopia incidence[195] in school-aged children.[196]

Technoference contributes to speech and bonding delays

Studies[116] of infant parental dyads find that more frequent reported mobile device use was associated with less room exploration and positive affect, and less recovery (i.e., engagement with mother, room exploration positive affect) even when controlling for individual differences in temperament. Delays in speech acquisition[197] and the development of interactive skills also have been reported in infants of parents that use devices more frequently. In addition, the phenomenon of "technoference"[198] is receiving increased attention from experts in behavioral and development psychology. Heavy parental digital technology use has been associated with suboptimal parent-child interactions. Parental problematic technology use—termed "technoference" — is associated with technology-based interruptions in parent-child interactions and potentially associated with a range of child behavior problems.

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Parental distraction in early infancy can be problematic for obvious reasons. This remains a topic of increased research attention and a matter that should be routinely queried at every well child visit, beginning with infancy throughout the school years. Simple questions noted below can provide the foundation for teachable moments that convey the need for direct parental involvement in early years when lifelong benefits can accrue. Harried young parents, especially those who are raising children without partners, may rely heavily on digital devices as a form of childcare. They should be informed about the importance of direct eye and verbal contact with infants, as well as reading aloud starting in infancy, as these practices have been shown to have lifelong benefits to social and emotional development.

Clinical practice guidance

Avoidable environmental exposures can profoundly affect and alter children's development and health. Along with the benefits of nutrition and regular physical and social activity, clinicians are aware of adverse effects of lead, pesticides, food additives, air pollution, ultraviolet radiation, and more broadly climate change, on children's health. Exposures that take place early life can have disproportionately large impacts on later life health and well-being.

As recommended by the AAP, clinicians can integrate developmental as well as EMF issues in practice

by regularly discussing screentime and digital media use. AAP guidance regarding phones and other wireless devices should be widely shared and employed. These include:

- For children under 18 months, avoid screen-based media except video chatting.
- For children 18 months to 24 months, parents should choose high-quality programming and watch while interacting with their children, on a limited basis.
- For children 2 to 5, no more than one hour per day of high-quality screen time and engage with children regarding content and experiences.
- For children 6 and up, establish consistent limits on the time spent using media and the types of media.

Recognizing that RFR may contribute to ill health provides further incentive to include clinical practices such as:

- Query use of screens, digital media, cell phones and Wi-Fi linked devices at yearly physicals;
- Provide guidance to patients and their families on how to decrease excessive screen time and to reduce RFR exposure (See Section 7);
- Respond with additional interview questions, resources and referrals as appropriate if symptoms potentially related to use of screens or exposure to EMFs are reported;
- Engage in continuing education and training on EMF issues, and screen use;
- Record and report cases where links have been identified between EMF and symptoms or health outcomes;
- Encourage undistracted reading out loud to infants and young children; and
- Develop family media plans for parents as well as children, explaining that parental distraction with devices can impair child development including speech acquisition.

Practitioners also need training in EMF-related effects to be able to discern whether common pediatrics complaints such as headaches and problems sleeping could, in fact, be due to the excessive use of technologies in the home or school environment. Clinicians encountering patients presenting with unexplained symptoms can consider the complete clinical picture and health history, and investigate, treat if necessary, or exclude commonly recognized etiologies. For example, patients may come into the office with unexplained array of symptoms such as headaches and rashes that may be related to EMF (e.g., cell antennas recently mounted nearby, or upgraded school Wi-Fi system recently installed). Clinicians need greater awareness so that in differential diagnosis they include the possibility that symptoms may be associated with EMF and evaluate the patient in a systematic fashion.

Clinical practice guidelines for EHS have been developed by trained clinicians and experts,[199] EUROPAEM group,[200] Dr. Riina Bray, Medical Director, Environmental Health Clinic, at Women's College Hospital, University of Toronto[201] and the Austrian Medical Association,[202] among others.

Clinical practice guidelines include:

- Comprehensive case history that includes environmental exposure history including questions regarding typical daily EMF/ RFR exposure, toxic metal exposures, diet, mold, and other potentially toxic chemical exposures at home, child care settings, school, work and play, and in the community.
- Assess community, work, school and home exposures to EMFs: proximity of cell phone towers, routers, DECT cordless phones, and any other wireless technology, especially in sleeping areas
- Assess variation of health problems depending on time and location. For example, do headaches or other unexplained symptoms attenuate in different areas, but return chiefly when the child is in one specific location? Did headaches or symptoms begin when a new router or cell antenna was installed?

As technologies (and healthier alternatives) evolve and knowledge advances, there is a need for clinicians periodically to update their knowledge through continuing medical education with technical experts in bioelectromagnetics—a field that is not widely taught or studied in medical schools at this juncture. Some accredited programs[203] offering up to 24.5 continuing medical education credits can be found online.

Electromagnetic sensitivity—An underdiagnosed pediatric problem

The phenomenon of hyper-reactivity to chemical and physical phenomena remains poorly understood but is believed to be a serious and sometimes disabling problem.

Electromagnetic hypersensitivity (EHS)[204] is believed to affect a small but significant segment of the population—with estimates up to 15%. Its prevalence in children has never been evaluated, but could prove to be important in cases in which vague symptoms of headache, numbness, tingling and rash cannot otherwise be alleviated. EHS is characterized by headaches, sleeping problems, memory problems, nosebleeds, unexplained skin rashes, digestive problems, neurological problems, heart palpitations and fatigue. Symptoms[200] vary from person to person, making this a challenging subject to study and to treat. Notably, prenatal and postnatal exposure to cell phone RFR is linked to increased headaches in children,[205] adolescents,[206] and adults,[205] and use of smartphones have been identified as a trigger for migraines.[207]

EHS symptoms[208] have been linked to exposures to non-ionizing EMF, including from nearby cell towers and base station wireless antennas and routers. No studies have been conducted on EHS in children. Dieudonné[209] studied forty individuals convinced that they were sensitive to electromagnetic fields, and concluded that contrary to allegations of nocebo responses, attribution of their symptoms followed a common linear model: (1) onset of symptoms; (2) failure to find a solution; (3) discovery of EHS; (4) gathering of information about EHS; (5) implicit appearance of conviction; (6) experimentation; and (7) conscious acceptance of this knowledge.

Further evidence of the importance of identifying sources of exposure and reducing them comes from a recent report from Sweden on the sudden acquisition of highly reactive biological responses to a newly introduced source of RFR. Following the introduction of 5G networks in a dense urban environment, a previously healthy couple reported disabling symptoms of headache, palpitations, tingling, tinnitus and major discomfort. Upon detailed examination of their environment, it was determined that 5G network had recently been installed quite close to their apartment. A thoroughly detailed case report[210] documents this sudden change in RF exposure and the onset of severe symptoms in this couple just a few days after the installation of a 5G base station on the roof above their apartment. The deployment of 5G caused a dramatic increase in maximum (peak) microwave radiation exposure, from 9 000 μW/m2 to >2 500 000 μW/m2. The symptoms quickly reversed when the couple moved to a dwelling with much lower exposure.

Symptoms often are misdiagnosed as health professionals lack training on the matter. Preliminary clinical practice guidelines[201] have been developed. The U.S. Access Board[211] has recognized that "electromagnetic sensitivities may be considered disabilities" under the Americans with Disabilities Act, and the Job Accommodations Network supported by the U.S. Department of Labor's Office of Disability Employment Policy has issued a list of guidelines[212] for accommodation of electromagnetic sensitivity.[213] Adults in the U.S. are often accommodated in the workplace (being provided hardwired computer connections, or moving to a lower-EMF office) but in many cases they have had to file legal actions.

The U.S. Access Board[211] has recognized that "electromagnetic sensitivities may be considered disabilities" under the Americans with Disabilities Act, and the Job Accommodations Network supported by the U.S. Department of Labor's Office of Disability Employment Policy has issued a list of guidelines[212] for accommodation of electromagnetic sensitivity.[213]

Despite these accommodations for adults, parents seeking accommodations in U.S. public schools for children who experience EHS have been challenging as schools will refuse to accommodate and the families often must resort to homeschooling. In the UK, parents won a legal battle[214] against local authorities who are now compelled to provide an environment with reduced wireless radiation so that their child can attend school. There are also other examples internationally of legal decisions mandating workplace accommodations or payment for injuries[215] from EMF exposure.

In Canada, EHS is described in the report, Medical Perspectives on Environmental Sensitivities[216] to the Canadian Human Rights Commission.[217] Medical and legal[216] reports underpin a policy[218] for accommodation under the *Canadian Human Rights Act.*

Synergistic and combined toxic exposures in children

Children are exposed to numerous combinations of environmental exposures over their lifetime. Even where exposures are low, they can interact with each other resulting in additive or synergistic results.

Animal and human studies[219] indicate that non-ionizing EMF can act synergistically when combined with other toxic agents. For example, Sueiro-Benavides et al.[220] found that 2.45 GHz, a frequency used in Wi-Fi networks, combined with carbon black (CB) increased CB-induced toxicity and prolonged inflammatory immune responses. Exposures to non-ionizing EMF from magnetic resonance imaging (MRI) or cell phones has been found to enhance the release of mercury from dental amalgam.[221] RFR has been found in several studies to impact the integrity of the blood-brain barrier that protects the brain from toxic molecules circulating in the blood.[132,222–225]

A longitudinal study[226] of 2,422 children at 27 elementary schools in 10 Korean cities examined effects and interactions between voice call cell phone use and blood lead levels (lead levels were comparable to those in U.S. children). Attention-deficit/hyperactivity disorder symptom risk was significantly greater in the children with above-median lead levels and above-median weekly cell phone call duration.

A similar interaction was reported by Choi et al.[227] Across the cohort, maternal cell phone use during pregnancy was not associated overall with child neurodevelopment during the first three years. Among children exposed to higher maternal blood lead level *in utero*, however, a greater risk of both a poorer psychomotor development index and a lower mental development index up to 36 months of age was associated with higher cell phone calling time or frequency during pregnancy.

A theoretical role for RFR in the etiology of autistic spectrum disorder

Autism remains a puzzling and troubling problem for growing numbers of children, their families and their physicians. The disease[228] is increasing among both males and females, and among nearly all racial/ethnic subgroups, from 4.2 per 1,000 in 1996 to 15.5 per 1,000 in 2010. A recent report from the U.S. Centers for Disease Control and Prevention notes that rates have continued to increase. The prevalence of autism spectrum disorder (ASD) among 11 surveillance sites is 1 in 54 among children aged 8 years in 2016 (or 1.85%). This constituted a 10% increase from 2 years previously when it was 1 in 59, and the highest prevalence since the CDC began tracking ASD in 2000. Consistent with previous reports, boys were 4 to 5 times more likely to be identified with ASD than girls. The rate for ASD is 1 in 34 among boys (2.97 percent) and 1 in 145 among girls (0.69%). Although many environmental factors[229] have been posited, including air pollution, pesticides, and heavy metals, the potential role of RFR should also be seriously explored.

Experimental studies showing that prenatal exposures to RFR can disrupt the development of the hippocampus provide some foundation for speculating that EMFs could also be a contributing factor. Thus, RFR has plausibly been hypothesized to play a role in the development of ASD via disruption of the developing poorly myelinated central nervous system. When presented with serious behavioral disorders including autism, some psychiatrists have employed successful treatment protocols that involve family management systems to facilitate cessation and withdrawal from use of digital devices. Psychiatrist Victoria Dunckley[192] notes that early use of digital devices can create a heightened state of fight or flight among young brains and bodies, placing them under constant stress. Children are easily addicted to routines of falling asleep, eating and even using the toilet accompanied, not by parents soothing assurances, but by digitized music, visions and sounds that increase dopamine—the brain chemical tied with pleasure and addictive behaviors. Providing several impressive case reports of toddlers that had been out of control and unable to give up their digital fixations, Dunckley notes that digital fasting can yield impressive results, especially with children on the autism spectrum. Her book provides several detailed instances where altering children's access to digital devices can radically improve behavior. Other published reports also offer corroboration for this hypothesized connection.[230,231]

Psychiatrist Martha Herbert and research analyst and editor of the *Bioinitiative Report*, an ongoing record of relevant scientific findings, Cindy Sage, among others,

have called for more aggressive investigation of the possible connections between RFR uses and exposures and disorders on the autism spectrum. They speculate that behaviors on the autism spectrum could emerge from alterations of electrophysiological oscillatory synchronization and EMF/RFR could contribute and "worsen challenging biological problems and symptoms; conversely, reducing exposure might ameliorate symptoms of ASD by reducing obstruction of physiological repair."[232,233]

Inadequate regulatory limits

FCC and ICNIRP regulatory limits have been long criticized by experts and the court because they do not address children's unique vulnerability, the biological and health effects of long-term exposure nor the current ways that children are exposed to cell phone and wireless radiation. In 2012, the AAP wrote the FCC and other federal agencies calling for an update to the FCC's 1996 exposure limits stating, "it is essential that any new standard for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure they are safeguarded throughout their lifetimes." A decade later that call remains unanswered.

Cell phone and wireless device limits

Regulations regarding human exposure to RFR include: 1. allowable limits for ambient exposures created by cell tower network emissions and wireless networks, called maximum permissible exposure limits in the U.S.; and 2. exposure limits for localized exposures into areas of body tissue from phones, and personal and household devices, referred to as Head and Body SAR limits. The ICNIRP and IEEE[38] standards used as the basis for many governments' limits remain largely unchanged since the 1990s and they are intended to protect for effects caused by short term high powered exposures. These limits are not designed to protect for effects from long term, low level chronic exposures because ICNIRP and IEEE do not consider such effects as "established." As former ICNIRP member James C. Lin describes them: "*They are flawed and are not applicable to long-term exposure at low levels. Instead of advances in science, they are predicated on misguided assumptions with outdated exposure metrics that do not adequately protect children, workers, and the public from exposure to the RF radiation or people with sensitivity to electromagnetic radiation from wireless devices and systems. Thus, many of the recommended limits are debatable and absent of scientific justification from the standpoint of safety and public health protection.*"[16]

Wireless network exposure limits

U.S. limits for RFR were promulgated by the FCC in 1996, based largely on a 1986 Report of the National Council on Radiation Protection & Measurements (NCRP)[234] and the Institute of Electrical and Electronics Engineers (ANSI/IEEE) C95.1-1991 standard.[235] The U.S. limits for environmental RF levels are among the most lenient in the world, and are similar to those of Australia, Japan, Germany and other countries that also adopted inadequate ICNIRP limits.

However, some countries, including Italy, Switzerland, China, and Russia have adopted regulatory limits for cell towers and base station network emissions that are far more stringent[236] than the thermally based limits of the U.S. FCC and ICNIRP.

European nations with more stringent regulatory limits set their policies based on the precautionary principle, a key framework used in their decision making process. This principle rests on the sage advice of Benjamin Franklin—better to be safe than sorry.

In 2011, the Parliamentary Assembly of the Council of Europe (PACE) Resolution 1815: The potential dangers of electromagnetic fields and their effect on the environment " [237] strongly recommends that the ALARA (as low as reasonably achievable) principle is applied, covering both the so-

In 2011, the Parliamentary Assembly of the Council of Europe (PACE) Resolution 1815: The potential dangers of electromagnetic fields and their effect on the environment " [237] strongly recommends that the ALARA (as low as reasonably achievable) principle is applied, covering both the so-called thermal effects and the athermic or biological effects of electromagnetic emissions or radiation."

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In contrast, the more strict RF limits in Russia and China[238] are considered "science based," not precautionary, and were developed based on their own government scientists' studies of the biological effects of nonthermal RFR levels. India lowered its limits to 1/10 of ICNIRP limits in 2012[239] in response to a report from an Inter-Ministerial Committee that reviewed the research[240] on impacts to wildlife, including honeybees and other pollinating insects, and concluded[239] that the "vast majority of published literature indicate deleterious effects of EMFs in various species." (See Fig. 7 for comparisons) It is notable that other groups have recommended even lower limits. For example, the Ecolog Report, commissioned by T-Mobile and Deutsche Telekom in 2000, reviewed the science recommended a limit of 0.01 W/m2 to" be rigorously adhered to by all base stations near sensitive places such as residential areas, schools, nurseries, playgrounds, hospitals and all other places at which humans are present for longer than 4 hours."[241]

Why the SAR standard is inadequate to protect children

Pre-market tests for cell phones and wireless devices measure the Specific Absorption Rate (SAR), which is the standard accepted measurement of the rate of RF (radiofrequency) energy absorption. (See Table 2.) For cell phones and other handheld wireless devices, many countries have adopted either FCC or the ICNIRP limits for premarket RF compliance. Although the FCC limit is slightly more restrictive compared to ICNIRP limits, both rest on avoiding the effects of heating as measured by the SAR.

The SAR metric is criticized as a heat-based measure unable to capture[72] the numerous characteristics[242] of nonthermal exposure considered relevant to bioeffects such as pulse, modulation, variability or duration of exposure.

That said, even if the SAR was a valid measure for health effects thresholds, the SAR testing protocol itself has long been criticized as unrealistic for numerous reasons. To start, it does not take into account the smaller sizes of women, infants and children, and other properties of children that place them at greater vulnerability. Thus, the child brain sits in a thinner skull that contains more fluid which can absorb more radiation per unit volume than the adult brain with its thicker skull.

In regards to children's exposure, the AAP[1] wrote the FCC in 2012 noting that, "although wireless devices sold in the United States must ensure that they do not exceed the maximum allowable SAR limit when operating at the device's highest possible power level, concerns have been raised that long-term RF exposure at this level affects the brain and other tissues and may be connected to types of brain cancer, including glioma and meningioma," and also that, "The current metric of RF exposure available to consumers, the Specific Absorption Rate, is not an accurate predictor of actual exposure."

The head and body phantom are filled with a homogenous liquid that does not capture the way the electromagnetic field moves through different tissues in the head such as brain tissue, which is of varying thicknesses and characteristics. The dielectric properties of tissues in children's head and brain differ from adults because children's tissues have more water content and thus are more conductive than adults.

The SAM model has long been argued to provide a conservative estimation of the exposure from a mobile phone, even for children. However, research supporting this position has generally used a scaled down version of an adult head which did not account for all age dependent variations in children, such the anterior fontanels which close between 7 and 18 months. When these more realistic variations are accounted for, the SAR values for children are significantly higher. For example, Mohammed[243] used realistic head models in several scenarios simulating young children between 3 months and 18 months holding phones near their ear and mouth as well as a person holding a mobile phone near a child's head. They found that 10g SAR values in the heads of young children are significantly higher than those for adults and also noticeably higher than the scaled models used in previous studies that considered dosimetry for children over 3 years old.

Research supporting the SAM model[244] is based on early phone models that were designed with antennas on the top of the phone body and more recent research has found that for newer phone models with antennas integrated along the bottom of the phone, the SAM does not always ensure[40] a conservative estimation.

Phones are tested while operating at the highest power level, in specific positions against the phantom head and body. Devices generally operate at the minimum necessary power, in order to maximize battery

life, but in many situations the power output is much higher, to ensure reception at the receiving antenna in the cellular base station. Low incoming signal strength triggers a significant increase a phone's emissions; people encounter low signal strength in rural areas far from base stations and also, for example, in rooms in basements or buildings where building materials block the signal. The many real world exposure scenarios result in highly variable emissions from any one cell phone model, regardless of the stated SAR value.

Although the standardized SAR test positions are supposed to simulate the way people typically hold a cell phone, the standardized positions do not test in body contact positions for body SAR tests. The test positions do not mimic a cell phone in full body contact such as in a pants pocket or resting against the abdomen. Parents today often hold their newborns with the cell phone right up against the baby and yet premarket SAR tests do not include such positions.

In summary, the SAR test and SAM have been roundly criticized as underestimating and not adequately capturing the real world exposures of children, babies, and toddlers, and children who are positioned in direct or close body contact with cell phones or other devices.

Furthermore, manufacturers SAR test phones at various distances from the body. In the U.S. a manufacturer can decide to test for body SARs at 5, or 10, or even 25 mm. The measured SAR value will increase the closer the phone is tested to the body phantom. Thus, the manufacturer posted SARs of different models that use different separation distances cannot be directly compared to each other.

Although SAR levels often are used to compare cell phones in terms of which phone emits more RF than others, the SAR value does not necessarily reflect a difference in a consumer's actual exposure for these reasons. Hence a phone with a lower SAR level does not necessarily mean lower RF exposure. Nonetheless, the SAR is the metric in use and the basis for exposure limits worldwide.

Regulatory gaps affecting children

The AAP[1] has long advocated[1] that federal agencies strengthen regulations calling for:

- A reassessment of human exposure limits and testing requirements to ensure children's unique vulnerabilities are addressed and to reflect the way children use phones today in close proximity to the body;
- Establishing a federal research program as the basis for exposure standards;
- Cell phone and wireless device product labeling requirements to "enable parents to better understand the potential dangers of RF energy exposure and protect their children."

The AAP supported[245] national legislation, the Cell Phone Right To Know H.R. 6358,[246] proposed in 2012, which would have addressed numerous regulatory gaps in federal policy regarding stating that, "Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults."

Prevention: medical organization, public health, government policy and actions to mitigate risk to children

Based on the established science, including children's special vulnerabilities, trajectories of exposures and diseases, clinicians need to know that they are supported by medical associations, have the resources to support their patients, and finally have the evidence in hand to advocate for them. A few of the supportive agencies and recommendations are noted below. Others can be found at www.ehtrust.org.[247]

Medical organizations and public health agencies

The AAP and several international medical organizations[248–251] have recommendations[252] on how to reduce cell phone radiation exposure. The AAP has long advocated for more protective[245] federal regulations and issued ten ways to decrease exposure in 2016[252] including "avoid carrying your phone against the body like in a pocket, sock, or bra. Cell phone manufacturers can't guarantee that the amount of radiation you're absorbing will be at a safe level."

"Avoid carrying your phone against the body like in a pocket, sock, or bra. Cell phone manufacturers can't guarantee that the amount of radiation you're absorbing will be at a safe level." American Academy of Pediatrics.[252]

In 2017, the California Department of Public Health (CDPH) released an advisory on cell phones.[253] CDPH's scientists had evaluated the RFR from almost[254] two dozen phones and found that when they transmit at their highest power due to use in areas of low service (one or two bars) the emissions can be up to 10,000-fold higher than when the phone is used in areas of strong signal. The CDPH's advice initially was based on the University of Pittsburgh Cancer Institute's 2008[253] cell phone radiation reduction advice to doctors and staff, constituting the first ever U.S. medical institution advisory on cell phone radiation.

In 2022, the Maryland State Children's Environmental Health and Protection Advisory Council[255] issued information on how families can reduce wireless and non-ionizing EMF exposures at home and also made recommendations to schools.

A summary of basic recommendations from these organizations and agencies is presented below.

"Avoid carrying your phone against the body like in a pocket, sock, or bra. Cell phone manufacturers can't guarantee that the amount of radiation you're absorbing will be at a safe level." American Academy of Pediatrics.[252]

How families can reduce EMF exposure

Cell phones

- Cell phones are not toys or teething items.
- When parents hold their babies or children in their arms, they should not simultaneously use or hold mobile phones or wireless devices as this will expose the child to RFR.
- Decrease overall time spent on wireless phones and prefer corded phones for long calls.
- Delay purchasing a first cell phone for a child. Cell phones should only be used by children for emergencies.
- Prefer text messaging over voice and video calls.
- Decrease exposure to and through the brain by using cell phones in speaker mode, away from the head and body, or wired airtube headsets with the phone away from the body. Avoid airpods. While Bluetooth signals are much weaker than cell phones, children and teens keep them in their ears for hours a day and the long term impact has never been independently evaluated.
- Avoid carrying cell phones against the body like in a pocket, sock, or bra.
- Do not talk or text while driving.
- Learn how to switch phone to airplane mode with Bluetooth, Wi-Fi, Hotspot antennas toggled off in settings. Many applications on phones can still be utilized in airplane mode. For example, in order to play movies and music but avoid unnecessary RFR exposure, download the files first, then switch the device to airplane mode and play.
- Keep an eye on your signal strength (i.e. how many bars you have). The weaker your cell signal, the harder your phone has to work and the more radiation it gives off. It's better to wait until you have a stronger signal before using your device.
- Avoid making calls in cars, elevators, trains, and buses. The cell phone works harder to get a signal through metal, so the power level increases.
- Learn how to connect the cell phone to the internet with ethernet cables.

Computer, laptop and tablet internet connections in buildings

- Install internet access via a hardwired ethernet connection instead of Wi-Fi.
- Wi-Fi routers should be distanced from areas where children sleep, play and school.
- At a minimum, power Wi-Fi networks off at bedtime and during periods when not in use.
- Connect computer/laptop/tablet accessories and peripherals such as printers, speakers, keyboard and mouse with cords, rather than Wi-Fi or Bluetooth.

At home

- Replace cordless phones with corded phones. Cordless phones and their base stations emit RFR.

- Avoid wireless digital baby monitors. If necessary, choose wired monitoring systems.
- Remove screens, electronics and wireless devices from the bedroom.
- Turn off devices at night and ensure sleep areas are not against a wall where utility meters are installed on the other side as "smart" meters are sources of RFR and other EMF.

Additional considerations during pregnancy

Simple preventive measures during pregnancy can significantly decrease fetal exposures, especially the high intensity exposures from a wireless device resting directly on the abdomen.

- Distance cell phones and wireless devices away from your abdomen.
- Power off cell phones when carrying them near your body.
- Always use laptops and tablets on a desk, not on your lap or close to your abdomen.
- For voice calls, use corded phones instead of cell phones or cordless phones.
- Use ethernet connections instead of Wi-Fi to connect devices.

Several governments, such as France, Israel, Greece and Switzerland have RFR measurement programs in place along with easy access to the data. For example, in France, the National Frequency Agency ANFR "Observatoire des Ondes"[257] posts online the RFR measurements taken numerous times a day in various cities.

Cell tower emission and ambient limits

As shown in Fig. 7 numerous countries such as India, Israel, Greece, China,[256] Russia and eastern European countries have RFR limits for cell tower network emissions that are much stricter than the limits of the US/FCC (although there is not always documented reliable monitoring or enforcement in every country). Australia, Japan, Italy and Switzerland have limits for areas such as schools and apartment buildings and areas where people spend several hours a day. Several governments, such as France, Israel, Greece and Switzerland have RFR measurement programs in place along with easy access to the data. For example, in France, the National Frequency Agency ANFR "Observatoire des Ondes"[257] posts online the RFR measurements taken numerous times a day in various major cities. Countries such as Greece and Israel have policies in place that specifically restrict the placement of cell towers near "sensitive areas" defined generally as schools and/or homes and hospitals and provide for online access to real-time radiation levels. Greece further restricts exposure to a stronger limit within 300 m of sensitive areas. Chile's "Antenna Law"[258] has established mitigation measures in areas with dense infrastructure and prohibits towers near "sensitive areas" defined as institutions serving children, the elderly, and the medically compromised. Again, monitoring and enforcement are not reliably determined in many instances.

At the local level, numerous municipalities in the U.S.[259] and other countries[260] have policies to restrict cell towers on school property and many communities have removed wireless antennas from school properties. For example, the Supreme Court of India upheld a decision by the High Court of the State of Rajasthan to remove installations on school properties and playgrounds.[261]

Several countries focus their RFR monitoring and oversight on children's areas. Brazilian Law nr 11,934 includes regulations[262] defining a critical area as the 50-meters-radius around hospitals, clinics, schools, day care centers, and facilities for the elderly. The RFR levels must be assessed within 60 days after the issuance of a license and then regularly re-evaluated. Like France, Brazil hosts an online map[263] with the country's RFR measurements. Greece's National Observatory of Electromagnetic Fields[264] has 500 sensors providing RFR level monitoring for schools and other sensitive areas. Further measures that are commonly implemented internationally are listed in Table 3.

Regulatory gaps in the U.S

At the federal level in the U.S., policy changes are needed to address numerous regulatory gaps regarding

TABLE 3. International policy to Increase transparency, ensure compliance and reduce cell phone and RF radiation.

Policy	Country examples
Public RFR exposure limits are more stringent than ICNIRP/ FCC limits	Italy, India, Israel, Croatia, Ukraine, Greece, China, Russia, Canada, Switzerland, Belgium, Bosnia Herzegovina, Grand Duchy of Luxembourg, Belarus, Georgia, Serbia, Slovenia, Montenegro, Bulgaria, Turkey, Liechtenstein, Tajikistan, Kazakhstan, Uzbekistan, Kyrgyzstan, Moldova, Kuwait, Republic of Moldova, Iraq
RFR monitoring program for cell tower/base station emission compliance and/or environmental RFR exposures.	France, Greece, Turkey, Spain, Romania, Serbia, India, Israel, French Polynesia, Croatia, Bulgaria, Tunisia, Malta, Brazil, Bahrain, Monaco, Bhutan, Senegal, United Kingdom, Australia, Spain, Austria, India, Israel, Gibraltar, Brussels Belgium, Switzerland, Norway, Lithuania.
Straightforward official government advice that the public and/ or children "should" minimize cell phone RF exposure.	United Kingdom, Russia, Switzerland, Finland, Ireland, Germany, Belgium, Greece, Israel, Turkey, Singapore, France, Denmark, India, Austria, Cyprus, Canada, Italy, French Polynesia - Maryland U.S. for Wi-Fi in Schools (CEHPAC), Korea, Sri Lanka, Croatia, Krakow Poland, European Parliament Resolution 1815
Ban on mobile phone advertising to children	France, Belgium, French Polynesia, Russia
Ban on sale of phones designed for young children	Belgium, France, French Polynesia
SAR labeling on device, packaging or by retailer at point of sale	France, Israel, India, Belgium, Russia, Korea
SAR levels for cell phone models are publicly posted on easily accessible government website	France, Korea, Austria, Senegal, Germany,
Market surveillance program for cell phone SAR compliance	France, Canada
Public awareness program, robust website and/or educational campaign to educate the public on how to minimize RFR exposures from cell phones	France, French Polynesia, Israel, Cyprus, Israel

all aspects of control, monitoring, measuring and remediating wireless radiation.

First, no federal agencies with health or environmental expertise have reviewed the totality of the science to ensure U.S. regulations are adequate. In 2021 the U.S. Circuit Court of Appeals for the District of Columbia issued a landmark ruling in the case of Environmental Health Trust et al. vs. the FCC[55] that challenged the FCC's decision not to update the human exposure limits for RFR emissions from cell phones, Wi-Fi, and cell tower networks. The Court found that the FCC did not provide evidence of properly examining scientific evidence on the record and had ignored studies indicating low level non-thermal exposures could cause harm, especially for children. The Court then ordered the FCC to provide a reasoned explanation regarding these issues:

- the impacts of wireless radiation on children;
- the health implications of long-term exposure to RF radiation;
- the ubiquity of wireless devices and the technological developments since the FCC last updated its guidelines;
- the cell phone radiation emission test methods that use heat measurements and allow a space between the phone and body; and
- the impacts of wireless radiation on the environment.

Another critical regulatory gap is that when considering cell tower network emissions, there is no U.S. agency with health or environmental expertise engaged in any funded activities regarding health effects.

Unlike other countries that are gathering data via countrywide monitoring programs, the U.S. has no active federal field measurement program for assessment, compliance, or enforcement regarding cell tower and base station antenna RF emissions. The last federal agency report on RFR measurements was compiled in 1986 by the EPA.[265] When companies apply to build a cell tower in the U.S. near a school or homes, there are no requirements for real world RFR measurements before and after the antenna facilities are built, nor any requirement for annual measurements. The computer simulations provided by the company do not always provide estimated RFR levels for all of the areas that will be impacted by the cell antenna installation, such as inside an apartment that shares a wall with a building mounted antenna, or inside the room of a school or home in direct line of sight of the main beam of an antenna. Such close

proximity installations can result in increased RF exposure[35,266,267] and are associated with various EMF-related symptoms.[208,210]

Although several nations post online maps with the location of cell towers and wireless facilities alongside RFR measurements, U.S. federal agencies neither collect, nor provide this information to the public. For example, small cell wireless facilities (such as those on poles less than 50 feet tall such as street lamps) generally do not need to be registered with the FCC.

International marketing, compliance and transparency measures

Some countries have enacted a variety of regulations designed to minimize children's exposure, ensure compliance with cell phone regulations, and ensure that the public has access to RFR information as shown in Table 3. For example, since 2010 France has prohibited the sale of cell phones designed for children under 6 years, and banned advertising cell phones to children under 14 years. In 2015, their cell phone labeling requirements were strengthened. Advertising must clearly recommend how to reduce exposure to the head or companies can be fined. In 2019, a joint order of the French Health and Finance Agencies[268] ordered that the cell phone consumer information should include several specific ways to reduce RF exposure to the brain, minimizing frequency and duration of use. In addition, the cell phone information includes "Keep radio equipment away from the belly of pregnant women," and "away from the lower abdomen of adolescents."[269]

2020 regulations[270] now mandate that computers, tablets and other handheld wireless electronics (as well as refurbished products) held close to the body were subject to the same labeling regulations as cell phones. In 2022, the French General Directorate for Competition, Consumer Affairs and Fraud Prevention found numerous violations[271] of their labeling requirements for wireless devices and issued over 200 warnings.

In 2014, Belgium implemented two Royal Decrees[272] that prohibited the sale and advertising of cell phones designed for children under 7 years old.[273]

Premarket cell phone and wireless device RFR testing

Some countries such as France and Canada perform independent SAR measurements of cell phone models to ensure regulatory compliance. Both countries have found that some phone models exceed their regulatory limits, even when tested at the manufacturer's stated separation distance, i.e. 5 or 10 or 15 mm from the head or body.

So far, over 35 non-compliant phone models have been either withdrawn from the French market or had software updates to decrease the RFR. The French National Frequency Agency, ANFR, posts their independent SAR test measurements for hundreds of cell phones online.[274] The U.S. does not have an oversight program for cell phone RFR emission compliance.

Furthermore, all cell phones and Wi-Fi devices such as routers, speakers, and gaming consoles have fine print instructions in their manuals stating that the user should maintain a specified minimum distance between their body and the phone or device in order to ensure compliance with regulatory safety limits.

Schools and child care settings

France, Israel, and regions in Belgium have removed Wi-Fi from kindergarten classrooms and restricted exposures in elementary classrooms. See Table 4. For example, French law (2015)[275] stipulates that Wi-Fi be off as the default setting, so that it is only turned on if needed for a particular classroom activity. The Parliamentary Assembly of the Council of Europe (PACE) Resolution 1815[276] (2011) recommends that "for children in general, and particularly in schools and classrooms, give preference to wired Internet connections, and strictly regulate the use of mobile phones by school children on school premises."

TABLE 4. International examples of policy measures to reduce RFR exposures in schools and child care settings.

Recommendations to prefer wired over Wi-Fi in kindergartens and schools	France, Israel, Germany, French Polynesia, Salzburg Austria, Maryland U.S.
Wi-Fi banned in child care settings and kindergarten	France, Israel, Ghent Belgium, French Polynesia, Cyprus
Wi-Fi off or minimized in elementary	France, Israel, Cyprus, Various municipal school districts worldwide

In the U.S., there are no specific school-focused or workplace-based federal regulations for RFR exposures. The Maryland State Children's Environmental Health and Protection Advisory Council report on Wi-Fi in school[277] recommends the reduction of RFR exposures in schools "as much as feasibly practical." Clegg et al.[278] outlines how to minimize RFR in buildings and includes the Collaborative for High Performance Schools[279] criteria to reduce RFR and ELF EMF in classrooms. (See a summary of recommendations below.)

Recommendations by Maryland Expert Advisors to the Governor and the Collaborative For High Performance Schools include:

- Install and use wired local area network (LAN) for internet access instead of Wi-Fi and connect classroom tech with cables whenever possible and always when building/remodeling.
- Ensure devices (tablets and laptops) are always used on a desk, not lap.
- Laptops, tablets and notebooks should have an Ethernet port and a physical switch to disable all wireless radios at once.
- Cell phones should be powered off and stored away during the school day. Wireless wearables should be turned to airplane mode.
- Prohibit use of DECT and cordless phones.
- Corded telephones should be installed in every classroom and there should be a way that students can contact parents and make calls during the day for planning purposes.
- Schools should integrate education on why and how to reduce RFR exposure into elementary, middle and high school class curriculum.
- Cell towers and wireless facilities should not be built on or adjacent/near to school property.
- Measure ELF and RFR levels in classrooms and sports areas yearly and when new technology is added to classrooms.

Healthcare settings

Sources of non-ionizing EMF exposure inside hospitals and healthcare facilities come from both the wireless networks (RFR) as well as electrical medical equipment (ELF-EMF).

EMF levels in neonatal units have been the subject of research due to the elevated exposure to an especially vulnerable patient group. Measurements of ELF inside incubators can range from 2 to 100 mG, depending on the distance from the top of the mattress to the electrical equipment.[280] After documenting higher levels of low frequency EMF levels inside closed incubators as compared to the ambient levels in the room, Penn State Medical Center researchers moderated the exposure through a grounding technique and found the mitigation improved infant's vagal tone, a marker of vulnerability to stress, and the risk of developing necrotizing enterocolitis.[281]

RFR in neonatal intensive care units primarily originates from staff and families' use of cell phones and wireless devices. A prudent avoidance strategy is recommended because these newborns are particularly vulnerable.[282]

In 2017, in Israel measurements of magnetic field EMF were taken for incubators in neonatal units at the request of the Ministry of Health and the Ministry of Environmental Protection[283] and they found a range from 0.05 to 5 μT. The Israel Ministry of Environmental Protection identified manufacturer approved efficient shielding methods to mitigate exposure in incubators and recommends reducing the duration of exposure as much as possible and prioritizing the use of low EMF incubators.

In Cyprus, the National Committee on Environment and Children's Health, under the auspices of the Ministry of Health, worked with the Archbishop Makarios III Hospital to pilot an RFR reduction program[284] in the pediatric intensive therapy unit and neonatal units. They removed the Wi-Fi access points, installed wired LAN networks and launched a multimedia educational program for families. RFR levels were measured before and after the mitigation and the measures resulted in a significant reduction in ambient exposure in the units.

The Agaplesion Diakonie Hospital in Hamburg, Germany has designed two "environmental" rooms for people with multiple chemical sensitivities and/or environmental allergies including sensitivity to electromagnetic fields. In addition to using low VOC emission building materials and fragrance free cleaning, several measures have been taken to reduce exposure to non-ionizing electromagnetic fields including the installation of power circuit breakers and prohibition of the use of cell phones.[285]

Recommendations for healthcare settings to minimize exposures, to support positive health outcomes as well as to accommodate patients with sensitivities:[13,83,197,199,215,275,281]

- Decrease RFR exposures in pediatric healthcare settings including waiting rooms, treatment areas, hospital rooms, and administrative workspaces by prioritizing wired connections and setting routers to their lowest operating settings;
- Ensure facilities have spaces with adequate EMF mitigation for treatment of sensitive patients;
- Educate patients, families, and staff;
- Utilize medical devices, equipment and technology designed without wireless features, or configured such that wireless connections are not essential and can be turned off when not in use; and
- Work with companies on research and design of safer technologies.

Conclusion: next steps for clinicians to better protect the young from impacts of RFR

Modern telecommunications have been embraced for their innumerable benefits to society, but we have been slower to acknowledge the need to avoid and reduce harms to youngsters or to the natural world on which our lives depend.[286] Fortunately, alternatives to employing wireless devices can provide safer, faster and more efficient technical performance for many modern applications. There are many distinct physical, psychological and sociological grounds for moderating children's screen time to promote healthy development. The principle of ALARA—as low as reasonably achievable—ought to be adopted as a strategy for RFR health and safety protection.

While such measures are being implemented in clinicians' offices, clinics and the like, there is a critical need for an independently funded training, research and monitoring program to identify major data gaps in the field which are substantial, to set relative priorities for research and training, and to conduct long term studies of the physical and psychological impacts of rapidly changing technological milieu, including ways to mitigate impacts through modifications in hardware and software.

The medical community has a critical role to play in the prevention and treatment of EMF associated illness. Steps that doctors and other healthcare professionals can take include:

- Federal level: Advocate with the AAP and other health professionals for a reassessment of RFR exposure limits and the development of standards that adequately address biological impacts, children's vulnerabilities and current use patterns.
- State level: Engage membership with educational and training activities as well as resolutions to support federal initiatives.
- Support policies that reduce EMF exposure for children in home, child care, school, health care, and recreational settings.
- Support the continued development of clinical guidelines for prevention, treatment and diagnosis of EMF related illness.

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