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NARRATIVE REVIEW

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Evidence base for yearly respiratory virus vaccines: Current status and proposed improved strategies

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Abstract

Annual vaccination is widely recommended for influenza and SARS-CoV-2. In this essay, we analyse and question the prevailing policymaking approach to these respiratory virus vaccines, especially in the United States. Every year, licensed influenza vaccines are reformulated to include specific strains expected to dominate in the season ahead. Updated vaccines are rapidly manufactured and approved without further regulatory requirement of clinical data. Novel vaccines (i.e. new products) typically undergo clinical trials, though generally powered for clinically unimportant outcomes (e.g. lab-confirmed infections, regardless of symptomatology or antibody levels). Eventually, the current and future efficacy of influenza and COVID-19 vaccines against hospitalization or death carries considerable uncertainty. The emergence of highly transmissible SARS-CoV-2 variants and waning vaccine-induced immunity led to plummeting vaccine effectiveness, at least against symptomatic infection, and booster doses have since been widely recommended. No further randomized trials were performed for clinically important outcomes for licensed updated boosters. In both cases, annual vaccine effectiveness estimates are generated by observational research, but observational studies are particularly susceptible to confounding and bias. Well-conducted experimental studies, particularly randomized trials, are necessary to address persistent uncertainties about influenza and COVID-19 vaccines. We propose a new research framework which would render results relevant to the current or future respiratory viral seasons. We demonstrate that experimental studies are feasible by adopting a more pragmatic approach and provide strategies on how to do so. When it comes to implementing policies that seriously impact people's lives, require substantial public resources and/or rely on widespread public acceptance, high evidence standards are desirable.

KEYWORDS
COVID-19 vaccines, health policy, influenza vaccines

1 | INTRODUCTION

Respiratory viral infections pose a significant burden worldwide. Influenza[1–3] and respiratory syncytial virus (RSV)[4] have been major seasonal contributors to massive hospitalizations and deaths every year. The recent 2020 pandemic caused by SARS-CoV-2 claimed millions of lives,[5] but the burden of COVID-19 has since declined significantly after widespread vaccination and naturally acquired immunity.[6] Despite major public health efforts, respiratory viral infections continue to place considerable strain on healthcare systems during the winter season, resulting in substantial socioeconomic costs.[7–9]

Today, yearly vaccination is widely recommended for influenza and SARS-CoV-2 in the United States. Most other countries generally target high-risk populations. Yearly vaccination programmes rely on updated vaccine formulations intended to target future, fall circulating strains. The regulatory basis for approval and justification for population vaccination is typically laboratory or serological experimental studies, followed by post-marketing non-experimental studies.

To lessen the annual burden of respiratory viral infections, both public health experts and the general population must know which preventive measures are most effective. The higher the level of certainty about their effectiveness, the stronger public health recommendations may be (for or against).

In this essay, we analyse and question the prevailing policymaking approach. We generally keep the discussion broad since considering the specifics of every vaccine would not significantly affect our argument; also, specific vulnerable subpopulations (such as those with autoimmune diseases or those who are immunosuppressed) may deserve special considerations[10–12] and these are outside the scope of this article.

We argue that well-designed and well-conducted experimental studies, particularly randomized trials, are necessary to address unresolved questions for effective vaccine policymaking. We focus on demonstrating how these trials can be feasibly conducted to render results relevant to the current or future respiratory viral season.

2 | ANNUAL RESPIRATORY VIRUS VACCINE DEVELOPMENT

2.1 | Influenza vaccines

The first influenza vaccine approved for non-military individuals was introduced in the United States in 1946.[13] In 1957, amid worries of the 'Asian flu', vaccination became available to the wider public.[14(p. 39)] In 1963–1964, a federal policy on influenza vaccination for the general population was formulated and has since been updated annually.[14(p. 39)]

The annual reformulation of influenza vaccines is challenging. Every year, the WHO, the U.S. Food and Drug Administration (FDA), the U.S. Centers for Disease Control and Prevention (CDC) and other public health experts collaborate to identify and select specific influenza strains for inclusion in the new seasonal vaccine, attempting to predict what the prevailing strains will be.[15] After strain selection, manufacturers with licensed influenza vaccines must quickly produce and distribute the updated vaccine.

The production timeline for egg-based and cell-based vaccines is approximately 6 months, of which the last 1–2 months are dedicated to regulatory validation and approval.[16–18] Recombinant vaccines have shorter manufacturing times, but availability of strain-specific reagents for vaccine potency and release tests may delay their commercial release.[19] Before approval, regulatory agencies verify the vaccine's identity and potency to ensure standardization. No additional clinical data is typically required, provided that the vaccine composition does not change (e.g. changing the number of antigens in the vaccine or the antigen dose, or adding an adjuvant).[20–23]

2.2 | COVID-19 vaccines

The first COVID-19 vaccines were developed in 2020 with unprecedented speed. Large randomized controlled trials (RCTs) were rapidly deployed, and few months later robust positive results led to emergency authorizations and subsequent full licensing. From 2021 onwards, the rise of immune evasive variants and waning vaccine-induced immunity[24] led to plummeting vaccine effectiveness against symptomatic disease (not necessarily severe disease), and booster doses were widely recommended.[25]

The first updated COVID-19 vaccines were developed and approved in 2022, supported by emerging real-world effectiveness studies and immunogenicity data. In January 2023, FDA advisors endorsed regular updates of COVID-19 vaccine strain composition.[26] In June 2023, an Omicron XBB.1.5-adapted monovalent vaccine was proposed for the 2023–2024 vaccination campaign.[27] In September 2023, the vaccine was ready for roll out. Regulatory approval was conceded based on mice immunogenicity data,[28–33] though later supported by observational research.[34]

3 | THE CURRENT POLICYMAKING APPROACH AND ITS EVIDENTIARY BASIS

3.1 | Influenza vaccines

Influenza vaccines have been advised on a large scale for decades through massive public health campaigns.[14] Annual vaccination for healthcare workers (HCW) was first recommended in 1984.[35] In view of low voluntary uptake, mandatory vaccination emerged. In 2004, the first mandatory seasonal vaccination policy for HCW in the United States was implemented.[36,37] Since then, influential organizations and medical professional societies, including the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America, have called for mandatory influenza vaccination of HCW[38]—which in fact became widely adopted in the United States.[39] Similar positions were taken in Canada.[40] In Europe, low coverage rates (<50%) are also commonplace, although mandatory vaccination is infrequent.[41,42] Some have even called into question the evidence supporting HCW vaccination as a patient safety measure.[43]

In 2018, Cochrane authors reviewed the evidence supporting influenza vaccines.[44–46] Specifically, the authors examined 50 trials in healthy individuals under 65 years old, 41 trials in healthy children and 8 RCTs in the elderly (≥65 years) comparing influenza vaccines with placebo or no intervention. While vaccines seemingly reduce the risk of influenza-like illness over a single season (from 2.3% to 0.9% in healthy adults, from 17% to 12% for live attenuated vaccines and from 28% to 20% for inactivated vaccines in children, and from 6% to 2.4% in the elderly), data are very limited on the prevention of hospitalization, death, transmission and absence from work. For instance, vaccinated healthy adults may have a small reduction in their risk of hospital admission, but the confidence interval (CI) is wide and crosses one (relative risk [RR] 0.96, 95% CI 0.85–1.08).[44] For the elderly, there is no data on hospitalizations, and the single randomized trial providing data for mortality and pneumonia was underpowered.[47] Generally, most estimates in the three reviews are graded low- or moderate-certainty evidence.

More recently, trials have focused on evaluating new vaccines or different strategies against what is considered the standard influenza vaccination approach at the time of the trial. However, the value of these trials remains limited: Either outcomes are clinically unimportant, that is, not patient-relevant (e.g. lab-confirmed infection, regardless of symptomatology and its severity or antibody levels, which are poor predictors of field protection[23]), the study design has limitations (typically non-inferiority) and/or follow-up is short.[48]

Midway through the influenza season, efforts are made to assess vaccine effectiveness. Test-negative studies, which use surveillance data, have been increasingly used for this purpose.[49–51] Vaccination rates are calculated among persons who test positive for influenza (i.e. 'cases') and persons with similar illness but who tested negative (i.e. 'controls'). The ratio of vaccinated to unvaccinated persons is then compared among cases and controls.

Despite the methodological limitations of test-negative studies, which we mention later, these studies have shown that influenza vaccines remain largely suboptimal at preventing infection and severe outcomes. From 2010 to 2023, the estimated adjusted vaccine effectiveness of influenza vaccines against influenza illness among the overall U.S. population ranged between 19% and 60%[52] (Figure 1). Specifically, during the 2022–2023 season, the CDC estimated overall vaccine effectiveness of 54%. Subsequent assessments yielded a lower value of 46%, being highest for children 6 months to 4 years (54%) and lowest among adults 65 years and older (27%).[53] Notably, estimations vary. In one study, protection against influenza A–associated hospitalizations was 23% and 41% among adults aged 18–64 and ≥65 years, respectively.[54] In a different study, the pattern was reversed —47% for people 18–64 years and 28% for those aged 65 and older.[54] Moreover, given the observational nature of the data, the estimates may be even more uncertain than the typical confidence intervals may suggest.

Despite influenza vaccines being largely safe, policies diverge. Since 2010, CDC advises everybody aged 6 months and older to receive an influenza vaccine ('universal' recommendation) on an annual basis.[55] In turn, the European Centre for Disease Prevention and Control (ECDC) encourages vaccinating high-risk groups only.[56]

3.2 | COVID-19 vaccines

The continuously evolving SARS-CoV-2 variants and the observed seasonal patterns[57] have earned COVID-19 a yearly influenza-like vaccination approach. In 2022, vaccination campaigns for seasonal boosters emerged.[58] In 2023, the seasonal vaccine was updated and its uptake strongly encouraged as part of annual fall/winter vaccination campaigns in the United States, United Kingdom, Australia and numerous European countries, including Sweden, Germany, France, Spain, Italy and Portugal.[59–67]

Randomized data on symptomatic disease allowed initial vaccine approval, yet pivotal trials were not powered to detect differences in hospitalizations or death, and did not include many frail elderly people or people with severe or multiple comorbidities. A few months after the first vaccine rollouts, short-term real-world

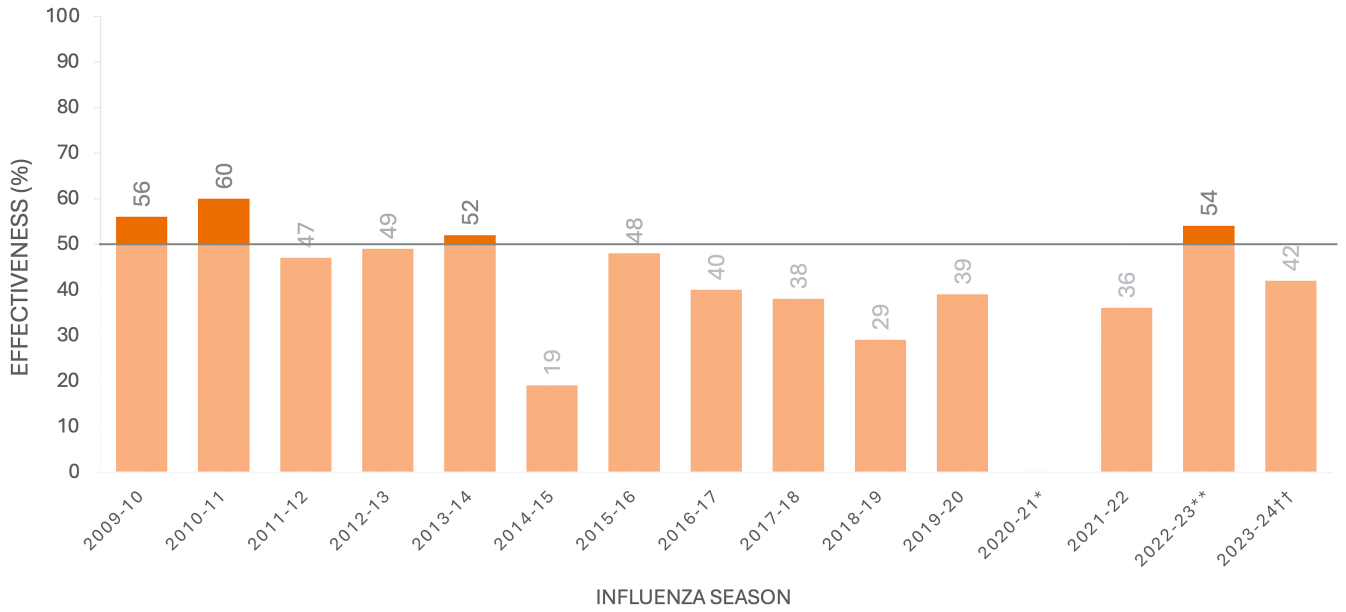

FIGURE 1 Effectiveness of seasonal influenza vaccines from 2009 to 2024, when most circulating influenza viruses were well-matched to those used in the vaccine products. Chart including vaccine effectiveness estimates from the United States Flu VE Network across influenza seasons. Data retrieved from Ref. [47]. The dark grey line marks the 50% effectiveness point to illustrate the fact that only 3 out of 14 VE estimates are over 50%. *2020–2021 influenza vaccine effectiveness (VE) was not estimated due to low influenza virus circulation during the 2020–2021 influenza season. **In a Wisconsin study among patients aged 6 months to 64 years, VE was 54% against medically attended outpatient acute respiratory illness (ARI) associated with laboratory-confirmed influenza A. ††VE estimates are preliminary.

observational data suggested that vaccination protected against severe outcomes with large effect sizes (generally over 80% effectiveness, which is substantially higher than that normally observed for influenza vaccines).[68,69] While such large effect sizes suggest that primary COVID-19 vaccination in 2021 did confer substantive protection against clinically important outcomes, the observational nature of the data should be kept in mind. The exact protection carries more uncertainty than what would have been achieved if these data had been confirmed in an adequately powered randomized trial. Moreover, the duration of the survival benefit is unknown. For example, if the survival benefit was derived mostly from frail people with limited life expectancy, its duration may be short since these people would die soon of other causes.

Additionally, the pivotal Pfizer/BioNTech BNT162b2 (Comirnaty) trial used a different manufacturing process than that used for the vaccines that were widely distributed—termed process 1 and process 2, respectively.[70] Process 2 was developed in order to upscale vaccine production. However, some have voiced concerns about the product quality and efficacy/safety of Process 2 vaccines.[70] Comparative immunogenicity and safety analyses were planned, according to a protocol amendment to the foregoing trial.[71] Nevertheless, to the best of our knowledge, results have never been published. These manufacturing process differences may cast some doubt into the Pfizer's trial results and which conclusions can be drawn from them.

Since the licensure of the first COVID-19 vaccines, observational data have been used to estimate vaccine effectiveness. In September 2023, the CDC concluded that vaccination of adults and adolescents with the 2023–2024 updated vaccine was beneficial based on pooled estimates from retrospective cohort or test-negative studies.[72] These estimates find relative risks of 0.5 for medically attended COVID-19 (95% CI 0.4–0.5) and COVID-19 hospitalizations (95% CI 0.4–0.7), and 60% lower risk of death (RR 0.4, 95% CI 0.3–0.6).

However, several aspects of the CDC's evidence review and conclusion raise concerns. All estimates were considered either 'low certainty' or 'very low certainty'. COVID-19 was not necessarily confirmed as the cause of hospitalizations. Absolute risk was calculated using the observed risk among a single observational cohort in the available body of evidence. The absolute risk reduction is relatively low—186 fewer COVID-19 visits, 53 fewer hospitalizations and six fewer deaths per 100,000. Finally, the studies included in the review evaluated vaccine effectiveness of the previous COVID-19 vaccine (bivalent Original and Omicron BA.4/BA.5).

A randomized trial of a third dose of the BNT162b2 mRNA vaccine versus placebo in 10,136 people who had previously received two doses of the vaccine showed spectacular short-term efficacy in lab-confirmed

infections (6 vs. 123 in the two arms, with median follow-up of 2.5 months), but no data on hospitalizations or deaths (only 1 death occurred, unrelated to the intervention).[73] Despite substantial heterogeneity in COVID-19 booster studies,[74] further observational analyses support the idea that repeated boosting reduces the risk of complications from COVID-19 in the short term, although vaccine-induced immunity rapidly wanes.[54,75,76] Among previously infected people, a study in the entire population of Austria showed small vaccine effectiveness for COVID-19 infections (17%) in the first 2 months that was reversed with longer follow-up to 8 months. There was no benefit for COVID-19 deaths, despite the results being biased towards overestimation of benefits due to healthy vaccinee bias (i.e. a propensity for healthier individuals to be more likely to get vaccinated than those who are less healthy).[77]

No published RCT has investigated to-date the benefits of COVID-19 boosters versus no boosters on clinically relevant outcomes (severe disease, hospitalization and death), and whether any potential benefits apply the same way to different groups. It is unclear whether healthy adults, young people and even the elderly benefit from receiving boosters now that almost everyone worldwide has already been previously infected.

3.3 | Both influenza and COVID-19 vaccines share a questionable policy approach

The fact that both influenza and COVID-19 annual vaccination policies rely on observational evidence is problematic. Observational studies are particularly susceptible to confounding and other biases (for an overview, see Ref. [78]), and there are complex difficulties faced by non-randomized studies in estimating the effectiveness of COVID-19 vaccines. The healthy vaccinee bias was particularly evident in a large 2021 cohort study reporting 94.6% lower mortality with COVID-19 boosters,[79] and in which non-COVID-19 mortality was also similarly 94.8% lower in those who received the booster.[80]

The test-negative design has been the observational design of choice for studying effectiveness of respiratory virus vaccines. Compared with other observational designs, test-negative studies reduce confounding and selection bias from health-seeking behaviour differences (like the healthy vaccinee effect), misclassification of case status and recall bias.[81]

However, the test-negative study design is still vulnerable to significant confounding, namely due to differential health-seeking behaviour, which typically inflates vaccine effectiveness.[48,82–86] For example, the design only includes persons who access healthcare services (in the US, unemployed individuals or people with limited insurance are less likely to seek healthcare, or vaccinated people may be more health-seeking and thus healthier) and ignores the prior exposure history of patients.[81] Or the cluster of symptoms that determines who gets tested for respiratory viruses may be narrowly restricted to certain respiratory symptoms or vary between places. Thus, true background rates of infection are unknown, and cases and controls are likely different populations at baseline.

In addition to these limitations, several important scientific questions remain unaddressed. These include the magnitude and duration of protection from different vaccine products or vaccination strategies, how effective vaccines are against new variants, the comparative effectiveness between different vaccine formulations, doses and/or vaccination schedules, and even the long-term immune consequences of repeated immunizations. In our view, because of persistent uncertainties, COVID-19 vaccination policies differ between countries, especially between the United States and several European countries. While the CDC has opted for universal vaccination recommendations, many European countries have targeted high-risk populations. In Table 1, we contrast fall/winter COVID-19 vaccination programmes for the 2023–2024 season across 10 countries.

Both influenza and COVID-19 are vaccine-preventable diseases to some extent, but the two conditions and their respective vaccines differ in several respects. Compared to influenza, COVID-19 exhibits a steeper age-related risk gradient for severity of disease,[89,90] as influenza carries greater global death burden for children.[91] Moreover, COVID-19 vaccines have greater effectiveness in unvaccinated people,[44–46,92] significantly more reactogenicity than influenza vaccines (Figure 2), and at least one serious, albeit still relatively understudied, safety concern, that is, myocarditis in the young,[99] though others have been raised (e.g. heavy menstrual bleeding with mRNA vaccines[100]). Moreover, there is little high-quality evidence that boosters further reduce severe disease and hospitalization among persons who previously had COVID-19, and most people have likely been infected at least once. These differences emphasize the importance of studying a policy approach for COVID-19 vaccination that considers individual aspects of the disease, rather than assuming that influenza vaccination policies can be equally applied to COVID-19.

Several experts have been critical of yearly COVID-19 universal vaccination policies. In 2021, two FDA regulators resigned in protest against universal boosting.[101]

TABLE 1 2023 fall/winter COVID-19 booster programmes in 10 different countries (northern hemisphere).

Country	Date	Recommendation
United States	12 September 2023	Updated COVID-19 vaccine* for everyone ≥6 months old (CDC recommendation)[58]
United Kingdom	26 May 2023 updated on 5 October 2023	Updated COVID-19 vaccine* for those at increased risk of serious disease from COVID-19: • Residents in a care home for older adults • All adults ≥65 years • Persons aged 6 months to 64 years in a clinical risk group (defined) • Frontline health and social care workers • Persons aged 12–64 years who are household contacts of people with immunosuppression • Persons aged 16–64 years who are carers and staff working in care homes for older adults (JCVI recommendation)[59]
Canada	11 July 2023 updated on 12 September 2023	Updated COVID-19 vaccine* recommended for those ≥6 months old, if it has been at least 6 months since last COVID-19 vaccine or infection. Immunization is strongly recommended—i.e. should be offered—for those at increased risk of COVID-19 infection or severe disease: • Adults ≥65 years • Residents of long-term care homes and other congregate living settings • Individuals with underlying medical conditions that place them at higher risk of severe COVID-19 • Pregnant • Individuals in or from First Nations, Métis and Inuit communities • Members of racialized and other equity-deserving communities • People who provide essential community services (NACI recommendation)[87]
Sweden	1 October 2023 updated on 16 November 2023	Vaccination against COVID-19 (vaccine composition unspecified) if: • ≥65 years • >18 years old and certain medical conditions (defined) • Never been vaccinated against Covid-19 and are ≥50 years • Pregnancy (>12 weeks) (Swedish Public Health Agency)[61]
Denmark	1 October 2023 updated on 25 October 2023	Updated COVID-19 vaccine* for: Persons ≥65 years • Persons below 65 years with some chronic conditions (defined) • Persons with severe obesity (BMI > 35) • Persons with other serious disease or conditions, e.g. persons with severe mental illness, Down's syndrome or severe abuse • Pregnant women in their 2nd or 3rd trimester if they have not previously received COVID-19 vaccination or carry other risk factors • Persons in the household of persons with congenital or acquired immunodeficiency and children at an increased risk of severe influenza or COVID-19 • Stem cell transplantation recipients should be offered two doses of Comirnaty Omicron XBB.1.5 given at a minimum interval of 3 weeks, followed by seasonal vaccination (a third dose) no less than 8 weeks after the second dose was given (Statens Serum Institut, Danish Ministry of Health)[88]

TABLE 1 (Continued)

Country	Date	Recommendation
Italy	14 August 2023 updated on 27 September 2023	Updated COVID-19 vaccine* in those with last dose >6 months, if: • Adults ≥60 years • Residents of long-term care homes • Pregnant women (any semester) or in post-partum period, including those breastfeeding • Front-line health and social care workers in hospitals, local areas and long-term care facilities; medical students or other students/interns rotating in healthcare facilities • Persons aged 6 months to 59 years, with high frailty motivated by concomitant/pre-existing conditions (defined) • Family members or carers of persons with severe frailty (Italian Ministry of Health)[65]
France	23 February 2023 updated on 10 October 2023	Updated COVID-19 vaccine* in those with last dose >6 months, if: • Person ≥65 years • Immunocompromised people • Pregnant woman • Resident in a residential care facility for dependent older adults and a long-term care unit • Person at very high risk of severe illness based on each individual medical situation and in a decision shared with health care teams • Person living in close contact or in regular contact with immunocompromised or vulnerable people, including health and medical professionals • ≥6 months of age with comorbidities Free vaccination is offered to all those who wish (French Ministry of Labor, Health and Solidarity)[63]
Germany	18 September 2023	Updated COVID-19 vaccine,* generally at least 12 months after the previous vaccination or infection, for: • Adults ≥60 years • Residents of long-term care facilities • Anyone over the age of 6 months with an underlying condition (defined) • People of all ages with an increased infection risk on account of their occupation in medical or long-term care • Family members and close contacts of people for whom the COVID-19 vaccination is unlikely to produce a protective immune response (STIKO, German Federal Ministry of Health)[62]
Spain	12 September 2023	Updated COVID-19 vaccine* for: • Persons ≥60 years • Persons ≥5 years old living in disability centres and nursing homes, as well as other long-term institutionalized people • People <60 years with risk conditions (defined) • Pregnant women (any semester) or post-partum period (Spanish Ministry of Health)[64]
Portugal	13 September 2023 Updated on 12 January 2024	Updated COVID-19 vaccine* for: • Persons ≥60 years • Residents and professionals of nursing homes and long-term care facilities • Those >12 years old with the comorbidities (defined) • Pregnant women ≥18 with comorbidities (defined) • Health professionals and care providers • Vaccination is offered to all those who wish (Direção-Geral de Saúde, Portuguese Ministry of Health)[66]

Abbreviations: ATAGI, Australian Technical Advisory Group on Immunisation; CDC, Centers for Disease Control and Prevention; JCVI, Joint Committee on Vaccination and Immunisation; NACI, National Advisory Committee on Immunization; STIKO, Standing Committee on Vaccination.

*2023–2024 vaccine formulation (Omicron XBB.1.5).

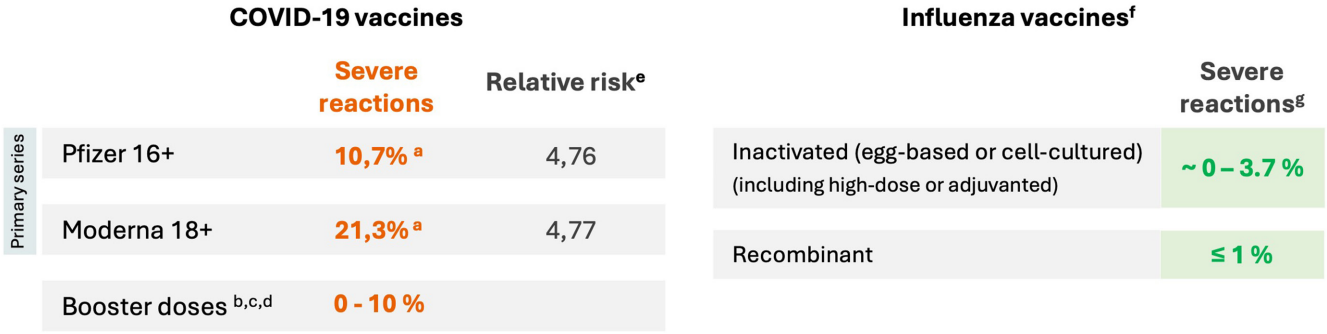

FIGURE 2 Comparative reactogenicity between COVID-19 and influenza vaccines in adults (grade ≥3, i.e. participant cannot carry out usual activities). Severe reactions with COVID-19 vaccines appear to be more common than with influenza vaccines, although data for recent COVID-19 boosters is limited. [a]Calculated from reported data in Ref. [93]. Reactogenicity data are from the original monovalent randomized controlled trials. The CDC evidence review considered that for subsequent or updated vaccines, data were very limited. [b]See Ref. [94]. [c]See Ref. [95]. [d]See Ref. [96]. [e]Relative risk to control arm. [f]No systematic review of influenza vaccines' reactogenicity is available, data are scattered and definitions vary. [g]Rough estimates based on a non-systematic review of available data, which include different types of influenza vaccines and different adult age ranges. See Refs. [97] and [98].

Paul Offit, one member of the FDA Vaccine Advisory Committee, has been publicly expressing his concerns.[102] In September 2023, Offit reiterated that vaccination policies should be focusing on high-risk groups, who are most likely to suffer serious disease.[103] Such a targeted approach is advocated by the WHO and several European countries (Table 1). In January 2024, two FDA leaders expressed regret over the low uptake of 2023–2024 respiratory virus vaccines in the United States, especially among the elderly (around 35% uptake), which is not seen in the United Kingdom, for instance.[104] These concerns deserve serious reflection about whether the push for universal vaccination with limited supporting evidence may be eroding trust in public health authorities.

4 | CLINICAL TRIALS ARE NECESSARY AND FEASIBLE

To reduce or resolve persistent uncertainties about the benefits of influenza and COVID-19 vaccines, additional experimental studies are necessary, especially RCTs. Randomization has the ability to adequately control for diverse known and unknown confounding factors.[105,106]

According to the principle of equipoise, trials can be conducted in a situation of uncertainty and/or disagreement among experts about the evidence regarding an experimental intervention.[107] To disturb equipoise, well-designed experimental studies are needed, even during public health emergencies.[108,109]

The COVID-19 pandemic showed that international collaboration and team efforts to implement large trials, like the WHO's SOLIDARITY or UK RECOVERY, could quickly generate practice-changing evidence within 6 months.[108] However, one may argue that 6 months far exceeds the time manufacturers have to run a trial testing the updated seasonal vaccine before regulatory approval and vaccine roll out, and indeed, this time horizon may be shortened with larger recruitment in RCTs.

For our purposes, let us draw a distinction between novel and updated influenza vaccines. Novel vaccines are new products, usually with a new composition (e.g. a different number of antigens, new antigen dose, new adjuvant) or novel manufacturing process, which undergo clinical trials before approval. Yet, these trials are problematic because they are often powered to show non-inferiority for surrogate outcomes such as antibody levels, when antibody responses are poor predictors of field protection.[23] To illustrate, the Fluzone® High-Dose vaccine was approved in 2009 for people over 65 years old because it proved to elicit higher antibody titres than the standard dose formulation.[110] In 2019, a novel quadrivalent formulation (Fluzone® High-Dose Quadrivalent) was licensed based on the demonstration of a non-inferior immune response at 28 days post-vaccination and comparable safety with respect to trivalent high-dose formulations.[111]

Updated vaccines, that is, vaccines which underwent strain update 'only' through the same manufacturing process, can be approved without clinical efficacy data.[21,23] For instance, the recombinant influenza vaccine Flubok® was first licensed in the United States in 2013 after meeting FDA's requirements for immunogenicity, effectiveness (against documented mild influenza illness) and safety.[112] The following year, the manufacturer reformulated the vaccine to include the latest circulating strains and the updated vaccine was approved for distribution based on non-clinical data, following

the standard process of annual updating of seasonal influenza vaccines.[21,113]

In both cases, what is most needed is robust effectiveness data on important clinical endpoints, such as severe illness, hospitalizations and death. This can be achieved in two different ways, depending on whether a novel or updated vaccine is being considered. In Figure 3, we propose a research framework for seasonal influenza vaccines that could secure high evidentiary standards. For novel vaccine candidates, phase III trials may start early in the season and must be powered for clinically relevant outcomes. With robust enrolment, these trials could yield

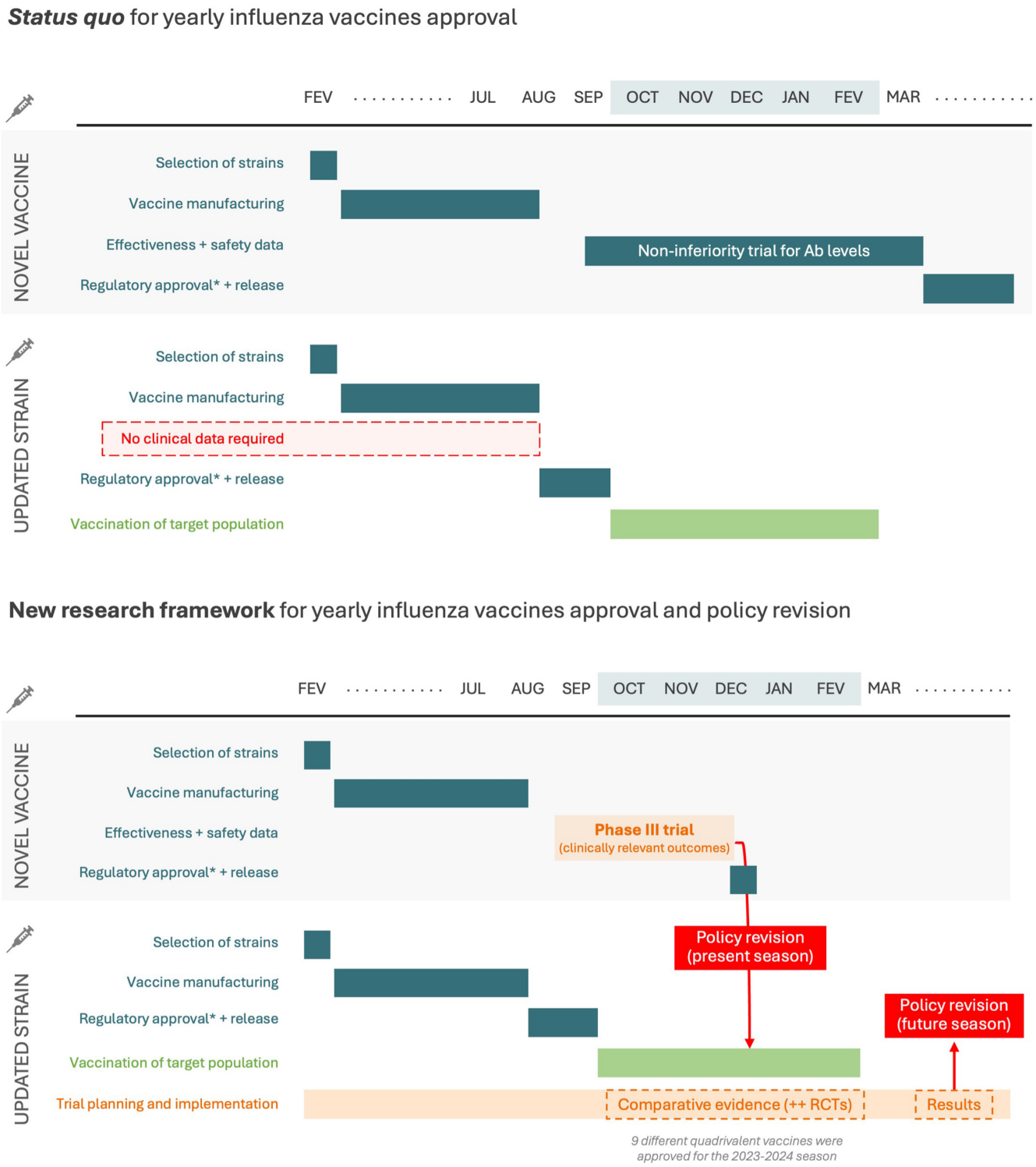

FIGURE 3 Research framework for seasonal influenza vaccines to secure high evidentiary standards for policymaking. Ab, antibody; RCT, randomized clinical trial; *Includes vaccine potency and release tests, as well as quality control; ++, preferably.

results in time to inform policy decisions within a single influenza season. For updated vaccines, well-conducted trials can compare multiple vaccine strategies during one season and encourage policy revisions for upcoming seasons. Different strategies may be compared for the same updated vaccine (e.g. different schedules) or, in some cases, between different updated vaccines (e.g. egg-based versus recombinant). However, it must not be assumed that all licensed updated vaccines have similar efficacy to one another.

In the quest of generating evidence as early as possible to inform about vaccine efficacy during an ongoing season, one should carefully think in advance about whether (and if so, when) interim analyses may be performed. Interim analyses need to anticipate adjustments in efficacy results, since early stopping generates inflated estimates of efficacy.[114] Genuine waning of efficacy over time should also be considered. To study the magnitude of the potential waning, one may need to avoid unblinding the trial after such early interim analyses. Regardless, the overall design, including the specific action plans after interim analyses, should be thoroughly vetted through ethical review and fully informed consent of participants.

This argument extends also to new or updated COVID-19 vaccines. Next, we suggest suitable clinical trial designs that can address uncertainties around respiratory virus vaccines and be feasibly conducted.

4.1 | Suitable and feasible trial designs

Pragmatic trials designed to inform about decisions in real-world practice[115] are particularly appropriate to address uncertainties around respiratory virus vaccines. Certain elements, such as adaptive and platform trial designs, cluster randomization and use of existing registries, can accelerate enrolment, address heterogeneous populations in real-life scenarios, accommodate complex interventions and potentially reduce overall research costs.[116]

While scarce, there have been pragmatic attempts at generating new, relevant and reliable evidence about influenza vaccines. A Danish research team conducted a pilot trial (DANFLU-1 trial) to investigate the feasibility of conducting a large-scale pragmatic trial in Denmark comparing two different dosing strategies in patients over 65 years old.[117,118] The results were highly encouraging. By integrating an individually randomized trial into routine seasonal influenza vaccination practice and using nationwide administrative health registries, the investigators achieved astonishing recruitment rates in the first 15 days—median of 674 patients per day,[119] approximately 11.4 patients per 100,000 inhabitants per day. Assuming the same population rate of enrolment in the United States one could imagine enrolment of 38,900 patients per day during the month of September. The ongoing DANFLU-2 trial aims to build upon DANFLU-1 with a multi-season study of >200,000 older adults powered for severe clinical outcomes.[120]

Countries with pre-existing nationwide population registries (e.g. several Scandinavian countries, Taiwan, and South Korea[121]) have an advantage in rapidly conducting large pragmatic trials, readily embedding them in their registries. These trials could then contribute to global decision-making. However, large-scale pragmatic trials can also be performed in countries lacking nationwide registries, such as the United States, by using other existing large-scale structures, for example, the military or healthcare organizations. For example, the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) trial is a 4-year randomized clinical trial of three FDA-licensed vaccine types (egg-based, cell-based and recombinant), designed to identify the most effective influenza vaccine platform for adults in a military setting.[122]

Cluster randomization has also been used. One trial evaluated the impact of care home staff vaccination on residents' all-cause mortality (rate difference: −5.0 per 100 residents, 95% CI: −7.0 to −2.0), influenza-like illness (−9.0 per 100 residents, −14.0 to −3.0) and health service use over two seasons (general practitioner consultations for influenza-like illness (−7.0, −12.0 to −2.0) and admissions to hospital with influenza-like illness (−2.0, −3.0 to 0)).[123] Another trial randomized 823 US facilities over a single season (2013–2014) to compare the effect of high-dose vaccines with standard-dose ones on hospital admissions among nursing home residents.[124] More recently, a Kaiser Permanente-based, industry-funded, study compared high-dose recombinant with standard-dose vaccines in adults ≤65 years old, including 1,630,328 participants over three seasons (2018–2021).[125]

For assessing comparative vaccine effectiveness in high-risk populations where hospitalization and death events are frequent, pragmatic trials can be run also with much smaller sample sizes, as in the case of a well-performed pragmatic trial comparing two influenza vaccines in 5260 patients with high-risk cardiovascular disease.[126]

These cases demonstrate that RCTs are feasible and not prohibitively expensive if one incorporates pragmatic elements. Most such trials may compare different active interventions or strategies, but comparisons against no vaccination are also possible, in settings and populations deemed ethically appropriate with equipoise. While

TABLE 2 Examples of unresolved research questions regarding respiratory virus vaccines and how comparative research could address them.

Research question	Description of research	Example of trial
What is the best type of vaccine product/route of administration for influenza vaccines? • Inactivated • Live attenuated • Live aerosol • Recombinant • Adjuvanted	Comparison between different vaccine products and/or routes of administrations, possibly in different populations	Multiarm, registry-based, RCT comparing inactivated high-dose, adjuvanted and recombinant in the elderly (65+) powered for clinically relevant outcomes Cluster RCT comparing adjuvanted vs. recombinant vaccines, against severe illness in the elderly (65+). Cluster randomization of vaccination facilities
Which outcomes do we want to prevent? • Viral specific outcomes • General health (ILI) and quality of life outcomes • Absenteeism	Powering trials for clinically relevant and/or public health related outcomes	Multisite (perhaps also multinational), placebo-controlled, cluster RCT testing the effectiveness of a given COVID-19 updated vaccine against severe illness, hospitalizations, and death in high-risk populations (65+ and those with pre-specified comorbidities) RCT in healthy adults or healthcare staff assessing working days lost
What is the magnitude of protection (against)? • Symptomatic infection • Severe disease/hospitalization • Death • Transmission (laboratory confirmation) • Absence from work • Other		RCT for effectiveness of COVID-19 boosters in older patients (50+), powered for severe disease and hospitalizations Cluster RCT for effectiveness of influenza vaccines to prevent in-hospital/nosocomial transmission; randomize different internal/general medicine wards to either staff vaccination or placebo during 1 or more seasons. Primary outcome: number of symptomatic influenza infections in patients; secondary outcome: days lost from work
What is the duration of protection? • Against asymptomatic/mild infection • Against severe disease	Testing via prolongation of control arms	Stepped wedge, 5-year, cluster RCT where HCW in different hospitals are randomized to annual influenza vaccination policy or no vaccination in a stepped way: every year, new hospitals are randomized to either annual HCW vaccination or no intervention. Outcomes: symptomatic infection in HCW, incidence of ED admissions for respiratory disease, incidence of in-hospital influenza infections
Which populations deserve special attention? • Children • Healthy adults • Healthcare workers • Older patients (50+) • Elderly (65+) • Immunocompromised • Other	Selection of special populations for study in different trials	(Any trial in this column; selecting one population that deserves special attention)
What is the best vaccine composition? • Trivalent (includes and targets 3 influenza strains) • Quadrivalent (includes and targets 4 influenza strains) • Universal (under development, targets all influenza strains) • Standard dose • Other doses • Weight-based dose	Comparison between different vaccine products, doses or regimens	Multiarm, adaptive, RCT comparing dose 1, dose 2, dose 3 and weight-based dosing of a recombinant influenza vaccine in a phase II/III design. In the phase III stage, the population is categorized into low- and high-risk and two interim analyses (IA) are planned. Each subpopulation is randomized to one arm. First IA = futility check (one subpopulations/arm may fail to continue). Second IA = another futility check + early efficacy claim

(Continues)

TABLE 2 (Continued)

Research question	Description of research	Example of trial
What is the best way of selecting strains? (hypothetical examples) • Algorithm 1 • Algorithm 2 • Algorithm 3, etc.	Comparison between different computer algorithms for predicting the most dominant strains in the upcoming season based on epidemiological data	RCT where vaccine manufacturers are randomized to either producing vaccines that include strains predicted by algorithm 1 (usual method) or by algorithm 2. Both vaccines are distributed. Outcomes: antigenic match to fall/winter circulating strain and clinical outcomes
What is the best vaccination schedule? • 6 months • 12 months • 24 months • Other	Comparison between different vaccination schedules	Cluster RCT comparing influenza vaccine effectiveness against severe outcomes in those scheduled for annual vaccination (12 months) and those for biennial vaccination (24 months)
Which setting confers higher risk of exposure? • Challenge • High risk environment (nursing home/ health care/ dorm) • Community	Comparison between different exposure settings	RCT, 2×2 factorial design, assessing symptomatic infection in healthy young adults living in dorms randomized to vaccination or no vaccination and then to either exposure (contact with influenza patients) or no exposure

Abbreviations: HCW, healthcare workers; ILI, influenza-like illness; RCT, randomized controlled trial.

including a placebo arm in future influenza vaccine trials is controversial, we suppose a placebo arm could be considered where evidence of vaccine effectiveness is most uncertain, in line with the ethical principle of equipoise. The same applies to COVID-19 vaccines. Given the absence of high-quality evidence that repeated boosting with updated COVID-19 vaccines protects against severe outcomes, even in high-risk populations, placebo-controlled trials may be deemed ethical. One may also argue that comparison of vaccines should be against no vaccination rather than a placebo, since 'vaccination or no vaccination' is precisely the pragmatic clinical decision that millions of people make each year and placebo trials have lower pragmatism.[127] Nevertheless, comparing vaccination to no vaccination in a trial setting is not devoid of challenges, in particular the risk of performance bias.

In running such trials, one should be aware of some residual caveats,[128] for example, trials using routinely collected data may provide lower estimates of effectiveness compared with traditional trials.[128,129] However, this can be anticipated in the sample size calculations. Moreover, observed estimates of effectiveness eventually may be more relevant about what can be achieved in real-world circumstances.

Platform trials bring promise to making respiratory virus vaccine research more efficient. One can envision multi-organizational and cross-company collaborative efforts to launch a platform trial where new vaccines are incorporated in the same trial structure as they become available, and where, among other adaptations, interventions are added or discontinued based on interim analyses.[130]

Table 2 lists a number of unresolved questions surrounding respiratory virus vaccinations along with proposed trials that could address these questions. Many of these trials test different strategies for mass vaccination campaigns—information that indirectly assess the effectiveness of seasonal vaccines. Ultimately, all of these strategies can be employed to yield a more information rich environment than the current system.

5 | CONCLUSION

In this essay, we demonstrated the necessity of generating strong evidence to support yearly respiratory virus vaccination, and have provided some strategies on how to do so. Current annual policies are supported by limited evidence. Manufacturers have little incentive to run RCTs powered for clinically important outcomes which might show their vaccines are ineffective—unless regulatory or public health agencies, who have the authority, require them to.

Probably policymakers will also march forward with RSV annual vaccination programmes. In 2023, RSV vaccines showed their first signs of clinical benefit in the elderly. Emerging data suggest that one dose of the adjuvanted vaccine could protect for more than one season,[131] which might have major implications for policymaking. Uncertainty about the duration of protection from RSV vaccines typifies a situation requiring proper investigation in an experimental setting.

We do not wish to reduce the complexity of policymaking and clinical decision-making to a matter of

running more RCTs. Different designs, randomized and other, can offer complementary evidence. However, healthcare policies and medical practices should be as best informed as possible. Scientists and policymakers should keep the bar high when implementing policies that seriously impact people's lives, require substantial public resources and/or rely on widespread public acceptance.

AUTHOR CONTRIBUTIONS

MB and VP conceptualized the article. MB wrote the first draft. VP and JPAI did substantial editing. All authors contributed to the writing, review, editing and analysis of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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