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BRIEF REVIEW ON ONGOING CLINICAL TRIALS ON COVID-19 VACCINES

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Abstract

Five years into mass deployment, COVID-19 vaccine R&D remains active, with trials now concentrating on variant-adapted boosters, mucosal (intranasal/oral) candidates aimed at blocking transmission, and broadly protective (pan-coronavirus) vaccines. Recent Phase 1–3 studies are refining antigen choice (e.g., KP.2/JN.1-era variants), delivery routes, and durability, while expanding evaluation in older adults and other high-risk groups. This review summarizes the current clinical pipeline and trial directions using the WHO vaccine landscape, ClinicalTrials.gov records, and recent peer-reviewed reports.

Keywords: covid-19, vaccine, WHO, clinical trials.

INTRODUCTION

While first-generation vaccines dramatically reduced severe disease and death, rapid viral evolution has driven iterative strain updates and next-gen platforms to improve mucosal immunity and breadth. The 2024–2025 development cycle formalized earlier strain-selection timelines for seasonal updates, and sponsors launched new trials to test 2025–2026 formulations, intranasal/oral candidates, and pan-sarbecovirus approaches. (PMC, World Health Organization) [1].

METHODS

We reviewed the WHO COVID-19 Vaccine Tracker & Landscape, screened ClinicalTrials.gov for interventional studies registered/updated in 2024–2025, and included recent peer-reviewed articles and institutional releases on intranasal/oral and pancoronavirus candidates. Searches were last performed August 29, 2025 [1].

The Active Clinical Pipeline in 2025

1) Variant-adapted boosters (updated mRNA and protein subunit):

Sponsors continue to test updated antigen formulations targeted to currently circulating lineages and to age-/risk-defined populations:

1. mRNA (Pfizer/BioNTech): an RNA-based variant-adapted booster study is ongoing to evaluate immunogenicity/safety versus prior formulations [2].
2. mRNA (Moderna mRNA-1283): a 2025–2026 formula trial in adults ≥65 years (and some younger high-risk strata) is assessing immunogenicity and safety—reflecting the shift to seasonal updates and targeted deployment [2].
3. Protein subunit (Novavax; Matrix-M adjuvant): continuing post-authorization/booster studies and record updates indicate ongoing evaluation of variant-specific lots and effectiveness endpoints [2].

These studies typically use neutralizing-antibody titers against contemporary sub variants (e.g., late-2024/2025 lineages) as primary endpoints, with teratogenicity and adverse events as key safety outcomes. Many include immunobridging designs to accelerate deployment [3].

2) Mucosal vaccines (intranasal and oral) to curb transmission

A major 2025 focus is stimulating local respiratory immunity to reduce infection and onward transmission:

A) **Intranasal, live-attenuated/viral-vectored**

1.) dNS1-based intranasal vaccine completed a randomized Phase 1 in children (China), showing acceptable safety and immunogenicity-supporting broader pediatric development [4, 5].

2.) Washington University–licensed intranasal candidate is entering U.S. clinical testing with dual deliveryroutes (spray and inhaled aerosol), aimed at eliciting robust mucosal IgA and tissue-resident T-cell responses [6].

3.) Patria (AVX/COVID-12) intranasal/IM booster reported Phase 2 immunogenicity and safety data from Mexico, adding evidence for mixed-platform boosting [7].

B) **Oral vaccines**

1.) Vaxart VXA-CoV2-3.3 is in an efficacy-oriented study assessing an oral tablet vaccine, with the appeal of needle-free administration and potentially improved acceptability/adherence [8].

Early-phase results suggest mucosal approaches are feasible; confirmatory field effectiveness against infection/transmission remains a central, ongoing objective [9].

3) Broadly protective and pan-coronavirus vaccines

Recognizing the limits of strain-by-strain updates, multiple groups are advancing pan-sarbecovirus/pan-coronavirus concepts:

1) CD40.Pan. CoV (France/Europe): aPhase 1/2a dose-escalation trial is testing a dendritic-cell–targeting platform designed to broaden B- and T-cell responses across sarbecoviruses.
2) ANRS LKV-PAN-01 (PanCoV) study (France): launched in mid-2025, this program evaluates an innovative French pancoronavirus vaccine candidate supported by national research agencies (ANRS-MIE/Inserm).
3) Stanford-led pan coronavirus program: developers reported first-in-human progress with plans for multi-country Phase 2 acceleration, indicating growing momentum of universal designs [10].
4) US early-phase pan-CoV trial (NCT06950177): a Phase 1 evaluating safety/immunogenicity of a pan coronavirus construct in healthy adults [11].

Collectively, these studies test conserved epitope targeting (e.g., mosaic nanoparticles, T-cell-centric constructs) seeking variant-agnostic protection. Strategic roadmaps (e.g., CIDRAP's) have prioritized such breadth by 2025 [12].

TRIAL DESIGN TRENDS AND ENDPOINTS

1. Population focus: Many trials now emphasize older adults (≥65 years) and risk-condition cohorts, aligning with current deployment strategies and the need for robust protection where severe outcomes concentrate.
2. Immunobridging & correlates: Neutralizing titers (live virus/pseudovirus) against current lineages remain central. Cellular immunity (polyfunctional T cells) and mucosal IgA assessments are increasingly included in intranasal/oral trials.
3. Effectiveness readouts: With high background immunity and fluctuating incidence, many studies use relative efficacy/effectiveness designs against updated comparators (e.g., KP.2-era mRNA) rather than placebo-controlled infection endpoints.
4. Safety monitoring: Ongoing pharmacovigilance and Phase 4 work continue for authorized platforms, alongside careful myocarditis/pericarditis surveillance in younger males and GBS monitoring for some non-mRNA platforms. (See WHO tracker's links to post-marketing evidence.)

Notable Representative Ongoing/Recent Trials (2024–2025)

1) **mRNA-based, updated formulations**
   a) Pfizer/BioNTech variant-adapted RNA booster-interventional study assessing updated antigen(s).
   b) Moderna mRNA-1283 2025–2026 formula-immunogenicity/safety in older adults.
2) **Protein subunit**
   a) NovavaxrS + Matrix-M-continuing variant-specific booster trials and record updates.
3) **Mucosal**
   a) dNS1 intranasal (Phase 1, pediatric)-randomized, double-blind trial completed, showing promising safety/immunogenicity.
   b) WashU-licensed intranasal (U.S. entry)-trial launching with nasal spray and inhaled routes.
   c) Vaxart oral tablet VXA-CoV2-3.3-efficacy-oriented study in adults.
   d) Patria (AVX/COVID-12) intranasal/IM booster—Phase 2 data published.
4) **Pan-coronavirus / Broadly protective**
   a) CD40.Pan. CoV (Phase 1/2a)-dendritic-cell–targeting approach.
   b) ANRS LKV-PAN-01 (PanCoV)-French clinical evaluation underway (2025).
   c) Stanford program advancing toward multi-country Phase II.
   d) NCT06950177 Phase 1 pancoronavirus vaccine (U.S.).

Key Scientific Questions Being Tested Now

1. Breadth vs. drift: Can conserved-epitope designs sustain neutralization across future variants without annual reformulation? Early trials (e.g., CD40.Pan.CoV; LKV-PAN-01) aim to answer this.
2. Mucosal immunity and transmission**:** Will intranasal/oral vaccines reduce infection and onward spread at the population level? Phase 1/2 safety and immunogenicity are encouraging, but field effectiveness remains the hurdle.
3. Durability**:** What dosing intervals are optimal for older/high-risk adults? Ongoing seasonal-update trials in ≥65s are collecting longer-term immunogenicity and breakthrough data.
4. Heterologous boosting**:** How well do mix-and-match strategies perform when combining mucosal with systemic platforms? Trials like Patria explore these hybrid schedules.

PRACTICAL CONSIDERATIONS INFLUENCING TRIAL DESIGN

Evolving regulatory and deployment contexts (e.g., seasonal updates, risk-based eligibility, and insurer coverage in some countries) shape enrollment and endpoints-favoringimmunobridging and non-inferiority designs over large placebo-controlled efficacy trials where incidence is variable and ethics are complex.

GAPS AND CHALLENGES

1. Correlates for mucosal protection are not yet standardized, complicating cross-trial comparisons.
2. Global representation, many current trials cluster in high-income settings; broader geographic testing is needed to address variant diversity and implementation realities.
3. Manufacturing and scalability for novel platforms (e.g., intranasal live-attenuated, mosaic nanoparticles) must mature alongside clinical validation.

OUTLOOK (LATE 2025–2026)

If mucosal candidates demonstrate meaningful infection/transmission impact in Phase 2/3 and if pan-sarbecovirus vaccines confirm broad neutralization and T-cell coverage policy could pivot from frequent reformulation toward broader, less frequent boosting for high-risk groups, complemented by mucosal boosters prior to seasonal waves. Continued use of the WHO landscape and trial registries will be essential to track these pivotal readouts.

CONCLUSION

Five years after the global roll-out of first-generation COVID-19 vaccines, clinical research remains highly dynamic, reflecting both the challenges of viral evolution and the lessons of large-scale deployment. Current trials illustrate three converging priorities: iterative strain-adapted boosters to sustain protection, mucosal vaccines to block transmission, and broadly protective constructs to achieve longer-term control beyond lineage-by-lineage reformulation. Trial designs increasingly emphasize older adults and high-risk groups, adopt immunobridging and effectiveness-based comparators over placebo controls, and integrate expanded safety surveillance. While early data from intranasal and oral candidates demonstrate feasibility, proof of population-level transmission impact is still pending. Similarly, pan-coronavirus strategies show promise in first-in-human studies but require validation of breadth and durability in larger cohorts. Key gaps include standardized correlates of mucosal protection, equitable global trial distribution, and scalable manufacturing for novel platforms. Looking ahead to 2026, the trajectory of the vaccine pipeline suggests a transition from frequent variant updates toward integrated strategies that combine systemic and mucosal protection with the ultimate goal of reducing infection, severe disease, and transmission in a sustainable manner.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT AND ETHICAL STATEMENT

Not Applicable

AUTHOR CONTRIBUTION

All Authors Are Contributed Equally

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