Assessment of the COVID-19 vaccine market landscape in 2021 relative to challenges in low- and middle-income countries

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ABSTRACT
To evaluate the early vaccine landscape relative to challenges faced by low- and middle-income countries (LMIC), we conducted a cross-sectional study of all COVID-19 vaccines in clinical trials in 2021 (n = 123) using a structured 13-point analytic framework. Supply sustainability was defined as a composite metric of four manufacturing and regulation variables. Vaccine desirability was defined as a composite metric of nine development and distribution variables. Ten vaccines in phases 2/3, 3, or 4 and five vaccines in phases 1 and 1/2 had a sustainability score equal to or above 0.5. Ten vaccines in phases 2/3, 3, or 4 and seven vaccines in phases 1 and 1/2 had a desirability score equal to or above 0.5. No vaccines in Phases 2/3, 3, or 4 met more than one distribution criterion. Structured assessment COVID-19 vaccine candidates in clinical trials in 2021 revealed numerous challenges to adequate access in LMICs. Key policy recommendations included increasing technology transfer to LMICs, developing international legal mechanisms to prevent export bans, and increasing investment in vaccine candidates with more favorable distribution profiles.

Introduction
By 6 August 2022, over 5.3 billion people had successfully received at least one dose of a vaccine against COVID-19.1 This tremendous accomplishment was achieved through unprecedented public and private investment in vaccine development, rapid scaling of manufacturing and cold chain capacity, sustained national and global regulatory body commitment, and swift implementation of complex distribution systems. Within two years of the World Health Organization’s (WHO) characterization of COVID-19 as a pandemic, there were more than 125 vaccines in clinical trials and nearly 200 in pre-clinical development.2 And by mid-2022, 9 vaccines had received emergency use listing (EUL) from the WHO.3 However, concurrently, there were extreme inequities between high-income (HIC) and low- and middle-income countries (LMIC). For example, 90.1% of people in Chile had received one dose compared to only 4.9% in Nigeria.1 COVAX, the vaccine pillar of the Access to COVID-19 Tools (ACT), is the multi-sector global collaboration to fund the development and equitable distribution of COVID-19 tests, treatments, and vaccines. COVAX cited export restrictions, vaccine hoarding, and delays in both manufacturing and regulatory approval as explanations for the unstable supply to LMICs in 2021.4 COVAX’s initial goal was also modest: coverage for roughly 20% of the population of participating countries by the end of 2021.5–6

The emergence of the Delta and Omicron variants further threatened progress toward global vaccine equity. In response, over 130 countries implemented vaccine booster programs, adding further strain on the global supply.7 The Omicron variant achieved a degree of immune escape from existing vaccines, resulting in increased reinfection and breakthrough infection, though disease severity was diminished.8–10 An additional dose was found to promote greater protection.11

The breadth and diversity of available and pipeline vaccines in 2021 also created challenges, particularly given the inadequate and uneven supply. Vaccine procurers had to make difficult decisions, balancing availability and affordability with efficacy, transparency, and distribution requirements. This was particularly true in LMICs that had less bargaining power with global pharmaceutical companies. Furthermore, LMIC challenges in healthcare delivery infrastructure, cold chain capacity, and biohazardous waste disposal could have been mitigated by a highly efficacious vaccine that was single-dose, stable at room temperature, and needle-free. Yet none of the available vaccines in 2021 had all these characteristics.

The goal of this paper was to evaluate the global COVID-19 vaccine landscape in 2021 relative to procurement and distribution challenges faced by LMICs. We aimed to identify best practices and unmet needs and provide key policy insights to inform the investment in and structure of rapid global vaccination efforts. The core of our analysis was a 13-point framework that analyzed vaccine supply sustainability and desirability for
all vaccine in clinical trials in 2021. Previously broad efforts have looked at the virological characteristics of leading vaccines. In contrast, this work provides a comprehensive assessment in the areas of vaccine development, manufacturing, regulation, and distribution.

Methods: sources & framework structure

Sources
We developed a two-dimension vaccine scoring system with 13 variables informed by the WHO Target Product Profile for COVID-19 Vaccines and extensive supporting literature. We identified vaccine candidates using the WHO vaccine tracker. The two primary data sources for vaccine characteristics were ClinicalTrials.gov and UNICEF’s COVID-19 Vaccine Market Dashboard. We also used Google News Alerts and ABI/Inform to identify press-releases, interviews, and business news that provided information on efficacy, storage temperature requirements, regulatory approval, manufacturing capacity, and additional manufacturing partnerships. All data and references are included in the Supplement.

Analytic method
The ‘supply sustainability’ dimension included four criteria that represent manufacturing strategy and regulatory status, such as multi-partner production strategy and WHO Emergency Use Listing (EUL). The ‘vaccine desirability’ dimension included nine criteria that represented vaccine characteristics that impact distribution and phase III clinical trial research strategy during vaccine development. For a full listing of the criteria and the rationale for inclusion, see Table 1.

The score for each dimension (R) was calculated by counting the number of variables that each vaccine met the criteria for (X) and dividing by the number of variables for which there was a known data point (Y). Variables for which the data point was unknown were counted separately for each dimension (Z). Regulation and development variables were not included for vaccines candidates in Phase 1, 1/2, and 2, except for the vaccine platform criterion (M). Vaccines with an R score of 0.5 or greater were considered highly sustainable or highly desirable. Vaccines that had at least one advanced purchase agreement with an optimal price (less than or equal to $10/dose) for LMICs or whose developers had indicated they would pursue optimal pricing were identified and labeled.

We present the framework results in the context of a comprehensive policy review. The policy review was conducted in consultation with senior researchers and policy experts. All analysis was conducted in excel and R version 4.0.5. All data in this paper is current as of 27 September 2021.

Results & discussion

Data availability, de-prioritization, & framework results
We identified 123 vaccines in clinical trials and 6 vaccines with an EUL from the WHO by 27 September 2021. We found substantial variation in the availability of information on the characteristics and strategies of each vaccine. This variation was most apparent by clinical trial phase (Table S1). Generally, vaccines in later phases had more information available.

Our study identified nine vaccines that were in use without full public disclosure of phase III clinical trial data. The following vaccines met our criteria for de-prioritization due to transparency concerns: Anhui (China), Cadila (India), Chumakov (Russia), CIGB-P52 (Cuba), Finlay-PS1 (Cuba), IMB & Chinese Academy (China), Kangtai (China), Sinopharm Wuhan (China), Vector (Russia). One vaccine, CureVac (Germany), met our criterion for de-prioritization due to efficacy concerns.

In the Sustainability dimension, we found ten vaccines in phases 2/3, 3, or 4 of clinical trials that scored 0.5 or above: AstraZeneca, Moderna, Pfizer, Janssen, Sinovac, Sinopharm Beijing, Gamaleya, Novavax, Bharat-IV, CureVac. Five vaccines in phases 1 and 1/2 had a sustainability score equal to or above 0.5: Arcturus, Serum, Condagenix, BiologicalE, and Cellid.

In the Vaccine Desirability dimension, there were ten vaccines in phases 2/3, 3, or 4 of clinical trials that scored 0.5 or above: Pfizer, CanSino, Vaxine, Razi, Clover, Moderna, AstraZeneca, Gamaleya, AMS-Walvax, and Arcturus-2. Seven vaccines in phases 1 and 1/2 had a desirability score equal to or above 0.5: Symvivo, ImmunityBio, University of Hong Kong, Bharat-VV, Vaxart, Imperial, and Codagenix.

Of the ten most sustainable vaccines, eight had pricing strategies that were optimal for LMICs. However, of the ten most desirable vaccines, only three had pricing strategies that were optimal for LMICs.

Manufacturing

Unpredictable success and setbacks in scaling production and fulfilling contracts on time
Manufacturing vaccines is a highly technical and expensive process that requires extensive quality controls and is subject to intense national and international regulatory scrutiny. This study identified many manufacturer-specific challenges with scaling vaccine production and fulfilling contracts on time. Decentralized production strategies, in which a developer uses multiple sites or production partners, mitigates the risk of production disruption. We found that most developers, except for those with vaccines in Phase 4, had fewer than four manufacturer partners (Table 2). All but one high sustainability vaccines in phases 2/3, 3, or 4 met both manufacturing criteria (Table 3).

Yet a decentralized manufacturing strategy did not guarantee avoidance of production delays. COVAX cited Sinopharm and AstraZeneca for a 15 million and 10 million dose reductions respectively due to production issues. Another impact on COVAX was the US FDA-mandated three-month production pause at Johnson & Johnson’s Emergent facility in mid-2021 which contributed to a 190,000 dose reduction (of a 1-dose course) in the COVAX supply forecast between July 2021 and November 2021. Predicting manufacturing setbacks is difficult. The key policy insight is that countries and international purchasing
Table 1. Standard assessment criteria & rationale.

| Criteria | Rationale |
|----------|-----------|
| **Supply Sustainability – Manufacturing** |  |
| (A) Prequalified Manufacturing Partner (>₁=1) | Proxy for Quality - The prequalified manufacturer designation indicates prior experience producing vaccines that met WHO quality standards. A manufacturing strategy that incorporates at least one prequalified partner will be able to leverage that prior experience and may be more likely to produce vaccines that meet quality standards.©
| (B) Multi-Partner Production Strategy (>₁=4) | Risk Diversification – Decentralized manufacturing avoids “single source dependency” though may be more expensive.©
| **Supply Sustainability – Regulation** |  |
| (C) WHO Emergency Use Listing (EUL) | Gold Standard - The WHO listing procedure is designed to expedite the availability of unlabeled medical products in a public health emergency while ensuring that efficacy and safety targets are met.© It is seen as a gold standard of emergency regulatory approval.
| (D) Authorization in Countries with National Regulatory Authorities (NRAs) deemed adequate by the WHO (NRA) (>₁=5) | Global Consensus – The WHO evaluates national-level regulatory authorities (NRAs) and designates those that meet strict criteria to be adequate for assessing quality of pharmaceutical production.© This variable counts the number of NRAs deemed adequate by the WHO (a functional NRA, stringent regulatory authorities (SRA), regional reference authority, or rated as maturity level 3 by the Global Benchmarking Tool) that have authorized each vaccine candidate. It represents the degree of global consensus among reliable independent assessors.
| **Vaccine Desirability – Distribution** |  |
| (E) Stable at Room Temperature (one month) | Ease of Distribution – “Higher storage temperatures and higher thermostability” are specified as “preferred” in WHO Target Product Profile for COVID-19 Vaccines.© Cold chain capacity and temperature requirements have been identified as a major challenge to vaccine distribution in LMICs.©
| (F) Single dose schedule | Ease of Administration - WHO Target Product Profile for COVID-19 Vaccines specifies preference for single-dose regimens.©
| (G) Oral or Nasal Administration | Ease of Administration - Eliminates accidental needle-stick risk and reduces disposal requirements, significantly easing distribution challenges.[67,68] The WHO Target Product Profile for COVID-19 Vaccines specifies preference for non-parenteral for “ease of rapid administration and other logistical issues.”©
| **Vaccine Desirability – Development** |  |
| (H) Double-blinded, placebo-controlled, randomized design phase III clinical trial (>₁=1) | Research Gold Standard – Double-blind, placebo-controlled, randomized design is the gold standard for phase III clinical trial research during public health emergencies.©
| (I) Multiple countries represented in phase 3 clinical trials (>₁=5) | Representation – Study populations should be representative of the population at risk.
| (J) Greater than 10,000 estimated participants in phase 3 clinical trials | Statistical Power – Larger studies generate more robust and reliable efficacy estimates and allow for more in-depth exploration of sub-group efficacy. The WHO has previously defined large as 10,000–30,000 participants.©
| (K) Efficacy >70% for symptomatic disease overall and by age, gender, and race or county | Efficacious Overall - WHO Target Product Profile for COVID-19 Vaccines specifies the critical efficacy threshold as 50% and the preferred efficacy threshold as 70% with consistent results in the elderly.©
| (L) Strong preliminary or robust evidence of high efficacy against severe disease, hospitalizations, or death | Highly Efficacious Against Severe Disease – Despite varying efficacies against symptomatic disease, most of the leading vaccine candidates were reported to be highly efficacious against severe disease (often 100%). This criteria accommodates the variation in secondary end-points between vaccines and the frequent presentation of efficacy against severe disease data as preliminary due to low numbers of severe cases in the control group.©
| (M) Capable of rapid response to variants (mRNA platform) | Streamlined Development and Rapidly Scalable – The mRNA vaccine development and manufacturing processes enable them to be more easily adjusted for new variants.©

bodies should pursue diverse acquisition strategies to mitigate the risk of production disruption. COVAX’s use of a diverse acquisition strategy likely mitigated further supply disruption.

**Need for greater public transparency in raw materials supply chain challenges and risks**

Vaccine development requires a network of suppliers of active and non-active ingredients, other materials, and equipment.© Even small disruptions can create significant bottlenecks and threaten global supply. Unfortunately, with few exceptions, developer- and manufacturer-specific public information on raw materials supply chain challenges and risks was not available, making it challenging to quantify the risk of supply chain disruption to equitable vaccine access.

Available evidence did reveal a strained supply chain. A market research company, BCC Research, found that active
The Sputnik V case demonstrates that technology transfer is not a solution that can be realized immediately. Building the infrastructure and training the staff necessary for specific LMICs to become regional providers of high-quality vaccines could require years of sustained investment. However, this investment would yield significant benefit beyond the pandemic context for both economic development and public health. This is particular true for mRNA technology as expanded local and global production capability could be used for future non-COVID-19 vaccines. Reluctance to share technology and knowledge is misguided and investment in manufacturing infrastructure in LMICs is both necessary and urgent.

**Manufacturing Key Insights**

- Best practice – Countries and international purchasing bodies used diverse acquisition strategies to mitigate production disruption.
- Unmet need – There is a lack of international raw material supply chain monitoring tools or frameworks to identify and remedy shortages and bottlenecks equitably.
- Unmet need – Vaccine production capacity in LMICs deserves immediate and sustained investment in LMIC vaccine production capacity with expanded use of technology transfer.

**Limited use of technology transfer to promote local manufacturing of vaccines in LMICs**

Throughout 2021, many voices in the global medical and scientific community called for increased technology transfer and expansion of local vaccine production within LMICs. Unfortunately, progress in this area was limited. Many pharmaceutical companies and high-income countries were against relinquishing intellectual property, citing a negative impact on innovation. One exception was the Russian Gamaleya Sputnik V vaccine which engaged in technology transfer in many LMICs including Lebanon, Turkey, Argentina, Egypt, Algeria, and India. However, despite this strategy, production remained low relative to expectation throughout 2021, with countries all over the world reporting delayed shipments. There were also some concerns regarding production quality.

**Regulation**

**Effective deployment of the WHO emergency use listing (EUL) procedure and the role of global frameworks**

By mid-2022, nine COVID-19 vaccines had been listed for emergency use by the WHO under 11 separate EULs. Six

| n | Phase 1 | Phase 1/2 | Phase 2 | Phase 2/3 | Phase 3 | Phase 4 |
|---|---------|----------|---------|----------|---------|---------|
| A | Prequalified Manufacturing Partner (> /= 1) | 1 (3%) | 3 (9%) | 0 (0%) | 0 (0%) | 6 (25%) | 5 (62%) |
| B | Multi-Partner Production Strategy (> /= 4) | 0 (0%) | 0 (0%) | 1 (12%) | 1 (9%) | 4 (17%) | 6 (75%) |
| C | WHO Emergency Use Listing (EUL) | - | - | - | 0 (0%) | 0 (0%) | 6 (75%) |
| D | Authorization in Countries with WHO-“approved” National Regulatory Authorities (NRA) (> /= 5) | - | - | - | 0 (0%) | 1 (4%) | 7 (88%) |
| E | Stable at Room Temperature (one month) | 4 (11%) | 5 (15%) | 0 (0%) | 2 (18%) | 2 (8%) | 0 (0%) |
| F | Single Dose Distribution | 2 (5%) | 3 (9%) | 2 (25%) | 2 (18%) | 1 (4%) | 1 (12%) |
| G | Oral or Nasal Administration | 8 (21%) | 2 (6%) | 1 (12%) | 0 (0%) | 1 (4%) | 0 (0%) |
| H | Double-blinded, placebo-controlled, randomized design phase 3 clinical trial (> /= 1) | - | - | - | 11 (100%) | 22 (92%) | 7 (88%) |
| I | Multiple countries represented in phase 3 clinical trials (> /= 5) | - | - | - | 0 (0%) | 3 (12%) | 6 (75%) |
| J | Greater than 10,000 participants in phase 3 clinical trials | - | - | - | 3 (27%) | 16 (67%) | 7 (88%) |
| K | Efficacy estimate >70% for symptomatic disease overall and within subgroups of age >65 years, male and female, and black or communities of color | - | - | - | 0 (0%) | 0 (0%) | 2 (25%) |
| L | Strong preliminary or robust evidence of high efficacy against severe disease, hospitalizations, or death | - | - | - | 0 (0%) | 3 (12%) | 5 (62%) |
| M | mRNA Platform | 6 (16%) | 4 (12%) | 2 (25%) | 2 (18%) | 1 (4%) | 3 (38%) |

Source: Assorted, Updated 9/27/2021.
(-) Metric not applicable for phase.
vaccines were listed by September 2021 and were identified as high sustainability vaccines in our framework (Table 3). Only one vaccine had a supply suspension – Covaxin produced by Bharat was suspended for Good Manufacturing Practice (GMP) deficiencies following a WHO post-EUL inspection in March 2022.43 This represents a successful implementation of the new emergency use listing procedure, which had been developed following the 2014–2016 Ebola outbreak to replace former guidance.22 More broadly, the success of the emergency use listing procedures exemplifies the need for prespecified, robust, and cooperative global frameworks that serve as guidance during public health emergencies. Collective and coordinated action is essential for developing and implementing equitable solutions for global problems.39 Other examples of important frameworks during the COVID-19 pandemic included the WHO’s public statement for collaboration on vaccine development and their target product profiles for vaccines.13,44

### Table 3. Highly sustainable vaccines.

| Name             | Price | Framework Results | Manufacturing | Regulation |
|------------------|-------|-------------------|---------------|------------|
|                  | LMIC Price | Score (R) | Missing (Z) | A | B | C | D |
| **Phase 2/3, 3, 4** |       |       |             |   |   |   |   |
| AstraZeneca      | $$     | 4/4    | 0           | - | - | - | - |
| Moderna          | 4/4    | 0      | -           | - | - | - | - |
| Pfizer           | $$     | 4/4    | 0           | - | - | - | - |
| Janssen          | $$     | 4/4    | 0           | - | - | - | - |
| Sinovac          | $$     | 4/4    | 0           | - | - | - | - |
| SinopharmBeijing | 3/4    | 0      | -           | - | - | - | - |
| Gamaleya         | $$     | 3/4    | 0           | - | - | - | - |
| Novavax          | 2/4    | 0      | -           | - | - | - | - |
| Bharat-IV        | $$     | 2/4    | 0           | - | - | - | - |
| CureVac           | 2/4   | 0      | -           | - | - | - | - |
| **Phase 1, 1/2**  |       |       |             |   |   |   |   |
| Arestus          | 1/2    | 0      | -           | - | - | - | - |
| Serum            | 1/2    | 0      | -           | - | - | - | - |
| Codagenix        | 1/2    | 0      | -           | - | - | - | - |
| BiologicalE      | $$     | 1/2    | 0           | - | - | - | - |
| Cellid           | 1/2    | 0      | -           | - | - | - | - |

Source: Assorted, Updated 9/27/2021.

CureVac’s efficacy is less than 50%. Table only includes vaccines with a sustainability score =/> 0.5. Green indicates criteria is met, gray indicates criteria is not met, white indicates missing data, (.) indicates metric not applicable for phase. The score for each dimension (R) was calculated by counting the number of variables that each vaccine met the criteria for (>x) and dividing by the number of variables for which there was a known data point (Y). Variables for which the data point was unknown were counted separately for each dimension (Z). $$ indicates the vaccine has an advanced purchase agreement with a price less than $10/dose or that the vaccine developer has a stated commitment of low pricing for LMICs. (A) Prequalified Manufacturing Partner (>x = 1); (B) Multi-Partner Production Strategy (>x = 4); (C) WHO Emergency Use Listing (EUL); (D) Authorization in Countries with WHO-“approved” National Regulatory Authorities (NRA) (>x = 5).

**Need for continued regulatory system strengthening in LMICs**

Strengthening regulatory capacity in LMICs is an urgent need to promote equitable access to safe and effective vaccines.20 The WHO estimates that 144 countries worldwide have sub-optimal regulatory agencies.45 This study found that many leading vaccines achieved regulatory consensus across many national regulatory authorities (NRAs), often in the context of a WHO EUL. However, ten vaccines maintained less than five NRA approvals throughout 2021, potentially indicating that assessment may have been inadequate in those countries.

Effective regulatory systems require that governance mechanisms, technical expertise, scientific tools, sustainable funding, monitoring, and performance assessment all align and operate in a coordinated manner.46 The WHO uses the Global Benchmarking Tool (GBT) to assess NRAs in several core areas including registration and marketing authorization, market surveillance and control, licensing, regulatory inspection, laboratory testing, clinical trial oversight, and lot release – a process that takes 2–5 years and allows countries to identify priorities for strengthening their regulatory programs.45,47 Given the complex nature of regulatory system strengthening, it is important to sustain effort and grow investment in this area over the long term.

**Vaccine nationalism and export bans**

National governments’ heightened concern for the wellbeing of their own population came at great expense to the overall
wellbeing of the global population, especially to those in LMICs. Many HICs epitomized vaccine nationalism by reserving enough doses to vaccinate several multiples of their population and stockpiling surplus for boosters.\textsuperscript{15,48} As of 25 March 2022, the United States had 3.2 billion doses reserved.\textsuperscript{15}

In early 2021, in the setting of rising infections, many European countries and India reduced vaccine exports to protect the supply for their own population.\textsuperscript{49,50} This had a large impact on the global supply of the AstraZeneca vaccine. At the end of the year, COVAX reported that they would most likely not receive any doses from the Serum Institute of India that year despite being promised 1.1 billion across 2021 and 2022.\textsuperscript{4} Given the negative impact of vaccine nationalism, it would be valuable to strengthen international legal mechanisms to prevent export bans from limiting supply to LMICs.

Regulation Key Insights

- Best practice – Global frameworks promoted collaboration and established guidelines for vaccine efficacy, safety, and regulatory approval.
- Unmet need – Regulatory systems in LMICs require continued partnership and investment to strengthen.
- Unmet need – Widespread vaccine nationalism and damaging export bans require mitigation with new international legal mechanisms centered on equitable distribution.

\textbf{Distribution}

\textbf{Need for greater priority and investment in promising vaccine candidates that are easy to transport, store, and administer}

The WHO Target Product Profiles for COVID-19 Vaccines in April 2020 listed single-dose, non-parental (no needle), and high-storage temperature stable vaccines as preferable.\textsuperscript{13} We found that no vaccines in Phases 2/3, 3, or 4 met more than one of these three distribution criteria. Two vaccines (Symvivo and ImmunityBio) in Phase 1 or 1/2 met all distribution criteria. Four vaccines (Vaxart, University of Hong Kong, VaxForm, and Bharat-VV) in Phase 1 or 1/2 met two out of three distribution criteria (Table 4).

In 2021, developers working on candidates that met two or more of these criteria were generally smaller, less well funded biopharmaceutical companies whose vaccines were in Phase 1, 1/2, or 2. Of these candidates, only one received funding from CEPI (University of Hong Kong) and none received funding from Operation Warp Speed. Significant investment coupled with technical assistance for large global clinical trials would have been beneficial for LMICs. This was a missed opportunity for partnership for major philanthropic or private global health equity-oriented organizations.

\textbf{Clear benefit to building distribution systems around storage requirements for existing vaccines early}

Vaccine development is high-risk, particularly during the first two phases. One study found that from 2005 to 2020, the probability of a vaccine progressing from phase 2 to licensure within 10 years was 10%.\textsuperscript{51} It is clear from our study that vaccine procurers should focus on building robust distribution systems for a diversified portfolio of existing, efficacious vaccines rather than waiting for the approval of vaccines with more ideal distribution characteristics. For example, during our research period the development of a promising Phase 1 candidate that met all three distribution criteria, Altmune, was suspended due lack of adequate immune response stimulation.\textsuperscript{52}

\textbf{Vaccine hesitancy}

While it was beyond the scope of our framework to examine vaccine acceptance, it is likely that distribution delays and reports of severe but very rare side effects (AstraZeneca, Janssen) contributed to vaccine hesitancy in LMICs. The Democratic Republic of the Congo delayed the roll-out of their vaccination campaign and South Africa suspended the use of AstraZeneca.\textsuperscript{53} A survey in South Africa found that this decision reduced the levels of trust in vaccines and in the vaccine development process.\textsuperscript{54}

\textbf{Distribution Key Insights}

- Best Practice – There was a clear benefit for countries and international purchasing bodies pursuing acquisition strategies centered around existing, proven vaccines as opposed to pipeline candidates.
- Unmet need – Vaccine storage and distribution characteristics need to receive greater priority in the early vaccine design process.
- Unmet need – Widespread vaccine hesitancy in LMICs and HICs requires continued efforts by local, national, and international public health authorities.

\textbf{Development}

Based on our framework, the Pfizer vaccine was the only Phase 2/3, 3, or 4 vaccine to meet all six development criteria. Moderna met all criteria with the exception of the multi-country representation in clinical trials. Other high sustainability vaccines met most of the development criteria except the target overall and sub-group efficacy.

\textbf{Inconsistent transparency between vaccine developers and a need for clear guidelines}

This study clearly documented significant variation in transparency between major vaccine developers (Table S1). There are many possible explanations. Manufacturing partners and distribution requirements may not be finalized until just prior to vaccine authorization and use. For example, we found that developers of 88% of vaccines in Phase 4 had disclosed the storage temperature compared to only 18% for vaccines in Phase 1. Public companies may also be more motivated to keep their shareholders informed than private companies or state-owned institutions. Countries with stronger regulatory systems may require greater public disclosure prior to authorization and use.

Furthermore, this study showed that nine vaccines were in use without full disclosure of phase III clinical trial data in a major academic medical publication. Vaccine developers do likely share privileged data on efficacy and safety during...
Table 4. Highly desirable vaccines.

| Name          | LMIC Price | Score (R) | Missing (Z) | Distribution | Development |
|---------------|------------|-----------|-------------|--------------|-------------|
| Pfizer        | $$$        | 6/9       | 0           |              |             |
| CanSino       | 5/8        | 1         |             |              |             |
| Vaxine        | 3/5        | 4         |             |              |             |
| Razi          | 3/5        | 4         |             |              |             |
| Clover        | 4/7        | 2         |             |              |             |
| Moderna       | 5/9        | 0         |             |              |             |
| AstraZeneca   | $$$        | 4/8       | 1           |              |             |
| Gamaleya      | $$$        | 4/8       | 1           |              |             |
| AMS-Walvax    | 3/6        | 3         |             |              |             |
| Arcturus-2    | 3/6        | 3         |             |              |             |

| Phase 1, 1/2 |
|--------------|
| Symvivo      | 3/4        | 5         |             | -            |
| ImmunityBio  | 3/4        | 5         |             | -            |
| University of Hong Kong | 2/3 | 6 | - | - | - | - |
| Bharat-VV    | 2/3        | 6         |             | -            |
| Vaxart       | 2/4        | 5         |             | -            |
| Imperial     | 2/4        | 5         |             | -            |
| VaxForm      | 2/4        | 5         |             | -            |

Source: Assorted, Updated 9/27/2021.

Only includes vaccines with a desirability score $\geq 0.5$. Green indicates criteria is met, gray indicates criteria is not met, white indicates missing data. (−) indicates metric not applicable for phase. The score for each dimension (R) was calculated by counting the number of variables that each vaccine met the criteria for (×) and dividing by the number of variables for which there was a known data point (Y). Variables for which the data point was unknown were counted separately for each dimension (Z). $\$$ indicates the vaccine has an advanced purchase agreement with a price less than $10/dose or that the vaccine developer has a stated commitment of low pricing for LMICs. (E) Stable at Room Temperature (one month); (F) Single Dose Distribution; (G) Oral or Nasal Administration; (H) Double-blind, placebo-controlled, randomized design phase 3 clinical trial ($>\leq 1$); (I) Multiple countries represented in phase 3 clinical trials ($>\leq 5$); (J) Greater than 10,000 participants in phase 3 clinical trials; (K) Efficacy estimate $>70\%$ for symptomatic disease overall and within subgroups of age $>65$ years, male and female, and black or communities of color; (L) Strong preliminary or robust evidence of high efficacy against severe disease, hospitalizations, or death; (M) mRNA Platform.

advanced purchase agreement negotiations. However, this is not a substitute for full public disclosure and the peer-review process. Rigorous independent review is essential. It enables the scientific and medical community to better interpret and contextualize the results. Transparency also engenders trust amongst the public.

It would be beneficial to cooperatively develop clear global guidelines for transparency throughout the clinical trial process and establish binding agreements between developers.

**Successful large national public-private partnerships for vaccine development with relative underfunding for efforts dedicated to global access**

One of the most significant early successes in the COVID-19 pandemic was the rapid development of multiple efficacious vaccines. The accelerated timeline was partly explained by the recent maturation of the mRNA platform technology, which had already benefited from over a decade of research. However, public-private partnerships also played an essential role by providing critical funding.

The largest public funding effort was the United States’ Operation Warp Speed, which dedicated $18 billion (USD) toward vaccine development with a focus on the needs of the US population. In Russia, the Russian Direct Investment Fund (RDIF), a sovereign wealth fund, invested in the Gamaleya Center that ultimately produced the Sputnik V vaccine. In Germany, at least $445 million was granted to BioNTech and $229 million to CureVac. And in China, Sinopharm is a state-owned entity.

The Coalition for Epidemic Preparedness Innovations (CEPI), the research and development arm of the ACT Accelerator, distributed $1.5 billion (USD) for COVID-19 research and development to 14 different vaccine candidates. Unlike the national public-private partnerships, CEPI funding required recipients to prioritize global access and affordable cost. The significant disparity in funding between inward-focusing national partnerships and outward-facing global initiatives likely provided incentives for pharmaceutical companies to prioritize contracts with high-income countries. In the future, increased funding for initiatives like CEPI would promote vaccine equity.

**Inconsistent use of early, large, multi-national clinical trials**

Historically, fewer clinical trials have taken place in LMICs relative to HICs. This trend continued in COVID-19-
related randomized controlled trials (vaccine and non-vaccine) with 84% of participants being recruited from high-income countries. Our study found that while many vaccines in Phase 4 during 2021 employed a global research strategy with clinical trials in more than five countries (75%), the majority of Phase 2/3 (0%) and Phase 3 (12%) vaccines did not.

Representation in clinical trials is key to ensuring population-wide safety and efficacy as estimates may differ by country due to differing characteristics of the population and of the circulating variants. The inclusion of multiple countries and diverse populations allows for findings to be more generalizable, for the sub-group analyses to be more accurate, and for first access to new vaccines to be more equitable. Public opinion of vaccines may also be supported by diverse representation.

Looking forward, it is crucial to promote greater access to vaccine clinical trials in LMICs. Specifically, developing infrastructure that enables smaller biotech companies to conduct broad multinational clinical trials would be particularly beneficial.

**Market saturation & reduced demand in high income countries**

In the first half of 2022, the rate of vaccine administration in high income and upper middle-income countries decreased substantially as market saturation was reached and demand decreased. In contrast, in low-income countries, market penetration was still limited. These contrasting market realities created additional challenges for vaccines still in earlier stages of development. The overall market opportunity had contracted prior to their release, further reducing financial and human capital investment. As such, it was likely that many of the vaccines in clinical trials at that time would not make it to market or would face limited distribution. This evolution speaks to the importance of prioritizing the needs of low and middle-income countries early in the vaccine development process to ensure that the vaccines that are most widely distributed throughout a pandemic are also the vaccines that meet the distribution challenges in low- and middle-income countries.

**Development Key Insights**

- **Unmet need** – Variation in developer transparency and use of vaccines without published Phase III clinical trial data warrants clearer guidelines and stronger enforcement.
- **Unmet need** – The challenges faced by LMICs require greater prioritization by the largest public-private partnerships.
- **Unmet need** – Smaller developers need improved ability to conduct large scale clinical trials in multiple countries.

**Limitations**

The primary limitation of this study was the variation in information availability between developers and lack of standardization in the reporting of vaccine characteristics. Many of the characteristics of each vaccine in our dataset were based on self-assessment by the vaccine developers and therefore may be inaccurate or inflated. This includes efficacy estimates and clinical trial phase, neither of which were independently verified. Our data is current as of September 27, 2021 and therefore does not include more recent changes to the market landscape. Some sources (e.g. press releases and early COVAX supply forecasts) were found to be no longer accessible online after our study timeframe ended. We elected to continue to cite these sources if they were the most current information within our study timeframe. Given market saturation in some markets and decreased demand overall, it is an unfortunate reality that many, if not most, of the vaccines in clinical development may not receive the necessary financial investment to become widely available. And lastly, our study design precluded the incorporation of country-level demand-side considerations such as variation in vaccine acceptance.

**Conclusion**

In conclusion, this cross-sectional study used public data and a structured framework to assess the 123 COVID-19 vaccine candidates in clinical trials in 2021 relative to procurement and distribution challenges faced by LMICs. Amongst vaccines in phases 2/3, 3, or 4, we found that 10 vaccines scored 0.5 or above in sustainability and that 9 vaccines scored 0.5 or above in desirability. No vaccines in phases 2/3, 3, or 4 met more than one of three preferred distribution characteristics defined by the WHO: single-dose, non-parental, and stable at high storage temperature.

These findings inform many policy recommendations for future rapid global vaccination efforts. First, vaccine procurers should pursue diverse acquisition strategies to mitigate unpredictable manufacturing supply disruptions. The supply chain should be made more transparent to allow procurers to better manage risk. Sustained investment in vaccine production capacity in LMICs is also a critical need. Second, within regulation, regulatory systems in some LMICs require strengthening to ensure that vaccines are approved for use only when safety and efficacy have been adequately established. There is also a critical need for new international legal mechanisms centered on equitable distribution to reduce the impact of vaccine nationalism and export bans.

Third, within distribution, vaccine storage and distribution characteristic suitability for LMICs needs to receive greater focus in the early vaccine design process. Vaccine procurers should continue to pursue existing, proven vaccines as opposed to pipeline candidates, even if the distribution characteristic profile is sub-optimal. Fourth, within development, efforts dedicated to global access should be better prioritized by large public-private partnerships. International clinical trials should include more representation from LMICs. And consideration should be given to the development of guidelines around developer transparency and the disclosure of essential information.

We hope that this framework and the ensuing policy insights can be used to guide future rapid global vaccine development and distribution efforts and better align investment and prioritization around the needs of LMICs.
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