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# An updated methodology to review developing-country vaccine manufacturer viability

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ABSTRACT

In 1997, Milstien, Batson, and Meaney published "A Systematic Method for Evaluating the Potential Viability of Local Vaccine Producers." The paper identified characteristics of successful vaccine manufacturers and developed a viability framework to evaluate their performance. This paper revisits the original study after two decades to determine the ability of the framework to predict manufacturer success. By reconstructing much of the original dataset and conducting in-depth interviews, the authors developed informed views on the continued viability of manufacturers in low- and middle-income country markets. Considering the marked changes in the market and technology landscape since 1997, the authors find the viability framework to be predictive and a useful lens through which to evaluate manufacturer success or failure. Of particular interest is how incumbent and potentially new developing-country vaccine manufacturers enter and sustain production in competitive international markets and how they integrate (or fail to integrate) new technology into the production process. Ultimately, most manufacturers will need to meet global quality standards to be viable. As governments and donors consider investments in vaccine producers, the updated viability factors will be a useful tool in evaluating the prospects of manufacturers over the mid to long term. The paper emphasizes that while up-front investments are important, other critical factors—including investments in a national regulatory authority, manufacturer independence, and ability to adapt and adopt new technology—are necessary to ensure viability.



## 1. Introduction

In 1997, Milstien, Batson, and Meaney analyzed the characteristics of vaccine manufacturers in developing countries and proposed seven critical factors to predict their long-term viability as suppliers [1]. Milstien et al. utilized the seven factors as a lens through which to recommend interventions such as strategic investments and increased political advocacy to address identified shortcomings in vaccine production facilities and operations. Since then, the framework and the viability factors have been used to assess vaccine manufacturers and shape global vaccine strategies.

Most developing-country vaccine manufacturers (DCVMs) in 1997 were state owned. As governments prioritized immunization and vaccines in the 1980s, local manufacturing seemed a natural step toward vaccine self-sufficiency. Milstien et al.'s working definition of viability, which was developed within the 1990s context of self-sufficiency, reflects this focus: "the ability of governments to provide for a stable sustainable supply of high-quality vaccines to meet national demand, for current and for future vaccines" [1]. Today, DCVMs have evolved into a blend of public, parastatal, and private-sector manufacturers, supplying vaccines domestically, to other countries, and to international procurers, particularly the United Nations Children's Fund (UNICEF) and the revolving fund of the Pan American Health Organization (PAHO). Given the shift from not only meeting national needs to also competing in international markets, we broaden the definition of viability to "the

*Abbreviations:* cGMP, current Good Manufacturing Practice; DCVM, developing-country vaccine manufacturer; EPI, Expanded Programme on Immunization; MNC, multinational corporation; NRA, national regulatory authority; PAHO, Pan American Health Organization; TRIPS, Agreement on Trade-Related Aspects of Intellectual Property; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

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long-term ability of a vaccine producer to reliably provide adequate quantities of high-quality vaccines at an affordable, and economically viable price to meet demand."

The widely held belief that life-saving vaccines should be sold at low, affordable prices to government and international procurement agencies places unique pressures on vaccine manufacturers, particularly given the difficulty and technical complexity of vaccine manufacturing compared with the production of other pharmaceutical products [2]. DCVMs are further challenged by changes in global market dynamics, increased sophistication of technological requirements, and the need for heightened regulatory rigor [3]. Furthermore, some manufacturers struggle with significant operational, quality, and managerial challenges.

Vaccine manufacturer viability continues to be important because immunization remains one of the most cost-effective health interventions to prevent deaths and illness from infectious diseases and saves millions of dollars of health care and other costs to society [4–6]. Using the framework set out by Milstien et al., we update the viability factors based on changes in vaccine markets, technological requirements, and regulatory standards since 1997. We then analyze the performance of manufacturers included in the original study according to their probable viability in 1997, updating the results of a seminal paper.

## 2. Methods

Through a literature search, we identified technological, regulatory, economic, and other developments that have affected DCVMs over the past 20 years and supplemented this information with data gathered during a series of qualitative interviews with experts. Table 1 summarizes key search terms and respondent profiles. With available resources that informed the primary dataset of Milstien et al., we assessed how the manufacturers in the original study fared over the 20-year time period. Using insights from this analysis, we confirmed and updated the viability factors, adapting the criteria to today's environment.

**Table 1**
Profiles of respondents in expert interviews and selected terms for literature search.

| Informant type | Number | Description |
|---|---|---|
| Technical experts | 5 | Experts included technical assistance providers to vaccine manufacturers, procurement agencies or funders, governments, and regulatory authorities. Areas of expertise included technical transfers, production, Good Manufacturing Practices, and business strategy |
| Procurement and technical assistance agencies | 2 | Manage pooled procurement and quality assurance on behalf of large donors and governments |
| Developing-country vaccine manufacturers | 21 | Manufacturers that supply to both national and international Expanded Programme on Immunization markets |
| Selected search terms for the literature search | Developing country vaccine manufacturers/Manufacturing, Emerging market vaccine manufacturers/Manufacturing, History of vaccine production/Manufacturing in developing countries, History of vaccine production/Manufacturing in emerging markets, Vaccine production/Manufacturing in: Africa/Asia/India/South America/Eastern Europe, Vaccine producer/Manufacturer viability, Vaccine, Producer/Manufacturer sustainability, Developing country vaccine markets, History of regulation of vaccines, WHO regulation of vaccines, History of Gavi, Good Manufacturing Practice (GMP), World Health Organization (WHO) vaccine prequalification process | |

## 3. Results

### 3.1. The evolving vaccine market 1997–2016

The dramatic growth in demand for traditional and new vaccines resulted in increased emphasis on ensuring a "healthy" vaccine market, defined as a market with adequate supply, reliable quality, and appropriate prices to meet global and national demands for new and existing vaccines [7]. The vaccine market grew from $3 billion to $41 billion from the mid-1990s to 2016, at the same time that regulatory, investment, and competitive pressures created new challenges for DCVMs [8–10]. The key drivers of change for the vaccine landscape and DCVMs over the past 20 years are as follows.

1. *Development and introduction of new vaccines:* Technological advances have led to the development of new vaccines over the past two decades, including rotavirus, pneumococcal conjugate, meningococcal conjugate, and human papillomavirus vaccines. Simultaneously, pressure to reduce the number of injections per child and the complexity of the Expanded Programme on Immunization (EPI) schedule have fueled the development and increased adoption of multivalent vaccines such as pentavalent vaccine (DTwP-HepB-Hib) and measles, mumps, and rubella combination vaccines. The number of vaccine antigens recommended by the World Health Organization (WHO) for inclusion in the EPI schedule continues to rise, from 6 in 1974, to 8 in 1997, to between 12 and 15 today, depending on the country. In addition, WHO recommends 11 other antigens for high-risk areas or populations [11,12].
2. *Increasing regulation:* As the vaccine market has evolved, so has the emphasis on high-quality production and safety of vaccines. Stringent current Good Manufacturing Practice (cGMP) standards, WHO prequalification requirements, and tighter oversight of and by national regulatory authorities (NRAs) require companies and countries to continually invest in equipment and facilities modernization and staff training to comply with quality and safety standards. The more robust standards increase the cost of vaccine production and largely define which markets manufacturers can enter. In addition, more rigorous enforcement of intellectual property rules with the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS), together with the harmonization of patent laws globally, creates a more challenging environment for DCVMs to access new vaccine production technologies [13].
3. *Gavi, the Vaccine Alliance:* Founded in 2000, Gavi has supported governments in 73 countries to introduce and expand coverage of high-priority childhood vaccines, thereby reducing the volatility of the EPI vaccine market and stabilizing demand forecasts [7]. As highlighted in Fig. 1, Gavi procurement (through UNICEF) has more than tripled in the past ten years to more than $1.7 billion annually, or about 4% of the global vaccine market value and about 2.8 billion doses [14,15]. In addition, UNICEF and its partners continue to improve procurement strategies, offering long-term contracts that enable them to negotiate lower prices earlier in a vaccine's product cycle [16]. Selling through UNICEF requires WHO prequalification, an intensive process to ensure vaccines meet global standards of quality, safety, and efficacy [17]. Achieving prequalification requires long-term commitment on the part of the firm and the host government (in development of an NRA), and only a limited number of DCVMs have been able to prequalify their vaccines.