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A cost analysis of producing vaccines in developing countries

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ABSTRACT

Developing country vaccine manufacturers (DCVMs) supply over half of the vaccines used in developing country immunisation programs. Decisions by developing countries to establish vaccine manufacturing should be based on economic viability, however reliable assessments of vaccine production costs are lacking. This study aimed to quantify the cost of establishing vaccine manufacturing facilities and producing vaccines in developing countries.

This study estimates vaccine production costs in developing countries based on twelve vaccines produced by eight DCVMs. The results were based on estimates of the capital and operating costs required to establish vaccine manufacturing facilities under three hypothetical scenarios of production scale and scope. Cost patterns were then compared to vaccine prices paid by countries in both industrialized and developing country markets.

The cost of producing vaccines in developing countries was estimated to be on average US$ 2.18 per dose, ranging between US$ 0.98 and US$ 4.85 for different vaccine types and formulations. Vaccine costs-per-dose decrease as production scale and scope increase. Cost-per-dose is mainly driven by fixed costs, but at a scale of production over 20 million doses per year it becomes driven by variable costs. Under the three hypothetical scenarios used, costs-per-dose of vaccines produced by developing countries were around 47% lower than vaccine prices in developing-country markets and 84% lower than prices in industrialized-country markets.

This study has found that local production of vaccines in developing countries exhibits both economies of scale and economies of scope. The lower costs relative to prices suggests that a producer surplus and potential profits may be attainable in both developing and developed country markets, supporting sustainable production.

1. Introduction

The need to secure a sufficient supply of vaccines is critical to ensure the success of immunisation programs. However, such investments must meet certain measures of cost efficiency to be economically justified. For a newly built vaccine production facility to be sustainable, the output and revenue must generate returns that can justify the investment. Investors, either governments or funding agencies, must be able to have a clear plan as to how long subsidies, if any, will be required and at what scale. An understanding of the costs to research and develop a vaccine will help countries estimate the required size of investments involved and evaluate the appropriateness of the prices achieved for vaccines produced.

Establishing vaccine production generally comprises three overarching components: (1) the establishment of a facility and acquisition of equipment; followed by (2) upstream processes involving pre-clinical and clinical trials at the start of a new production; this process depends on whether the vaccine technology used is novel or reinvented from originating/existing products;

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and (3) once completed, there are two manufacturing phases – bulk vaccine production and filling processes (Fig. 1).

While several studies estimate vaccine production and development costs [1–4], only two published studies have quantified the cost-per-dose of vaccines produced by developing country manufacturers [5,6]. This study adopts an approach to assessing cost drivers that is similar to these two studies, but for a larger number of countries and vaccine types. The aims of this study were firstly, to calculate the costs-per-dose of establishing local vaccine production in developing countries based on data provided by existing vaccine producers; and secondly, to quantify the variability of these costs across different driving factors, namely production scale and scope, as well as vaccine technology and formulation types. The study finally aims to compare costs to vaccine pricing to establish profitability of developing countries' vaccine manufacturing. The findings will assist non-producing developing countries in developing their plans to establish new vaccine manufacturing facilities, by estimating the cost required to establish a new vaccine facility and to bring a vaccine to market.

2. Methods

2.1. Data collection

Given the commercial sensitivity of vaccine production cost data, this study used a questionnaire for data collection based on self-reporting of cost figures in the form of ranges. The questionnaire was developed based on the existing literature and industrial practice regarding vaccine cost estimations [5–7]. The ranges for the cost estimates in the questionnaire were based on existing assumptions in the discipline. It was designed to ensure comparability of the data collected across different companies, which is important given that different cost accounting methods are used in different companies and different tax policies exist in different countries [8,9]. The questionnaire is presented in the Appendix.

Ten vaccine producers were contacted during an annual meeting of the Developing Country Vaccine Manufacturing Network (DCVMN) to maximise efficiency. Of these, nine manufacturers provided data, and of these, eight were DCVMs. The completion of the questionnaire was unsupervised and followed up via face-to-face and postal methods for clarification and confirmation of responses and assumptions used in the study. The responses were aggregated by vaccine technology and formulation categories as indicated in Gomez, et al. [10], for comparability as well as anonymity purposes.

Each respondent was asked to identify a specific vaccine product and estimate three types of costs associated with production of that vaccine. The first was fixed costs associated with facility and equipment costs and the second was development costs, which are semi-fixed costs. These two are categorised as capital costs. The third was variable costs related to bulk-dose release and fill-finish costs for a single unit of vaccine produced.

2.2. Capital costs

The respondents were asked to indicate, based on their experiences with fixed costs, estimates for three different hypothetical scenarios of production of scale and scope, assuming greenfield production, where building facilities are set up on completely new infrastructure. These scenarios were:

Scenario A: A production scale of 20 million doses per year, producing 1 vaccine;

Scenario B: A similar set up as in Scenario A, but producing five vaccines instead of one. This scenario allowed assessment of shared costs from producing more vaccines in a single facility. Potential cost savings arising from this scenario were identified as economies of scope;

Scenario C: A much larger production scale of 100 million doses per year, for the same number of vaccines as Scenario B (5 vaccines). This allowed estimation of the potential cost savings of a much larger production scale than in scenario B, identified as economies of scale;

In estimating fixed costs, manufacturers were asked to provide figures that included buildings, equipment, quality control (QC) laboratories, utilities, administration, and office space. The scenarios above were only applied to fixed cost estimations, and are reflected in the resulting annualised capital costs and total average costs-per-dose.

An additional **Scenario D** was presented to respondents, which assumes brownfield production (that is, production using an existing facility) [11,12]. In this scenario, the production scale was for 100 million doses of one additional vaccine. This scenario did not provide a direct comparison with the production scale and scope of the other scenarios, therefore the estimates will be presented separately as a fixed cost figure (Fig. 2).

As for semi-fixed costs, in the context of vaccine production in developing countries, DCVMs do not typically expend R&D costs to develop novel vaccines, for which very large sums of money are spent on preclinical studies. For semi-fixed costs, respondents were asked to provide estimates for the R&D cost of bringing a vaccine product to market, assumed to have been incurred in-house. This includes costs on personnel, pre-clinical and Phase I, II, III clinical trials, and supplies. Respondents were also asked to estimate

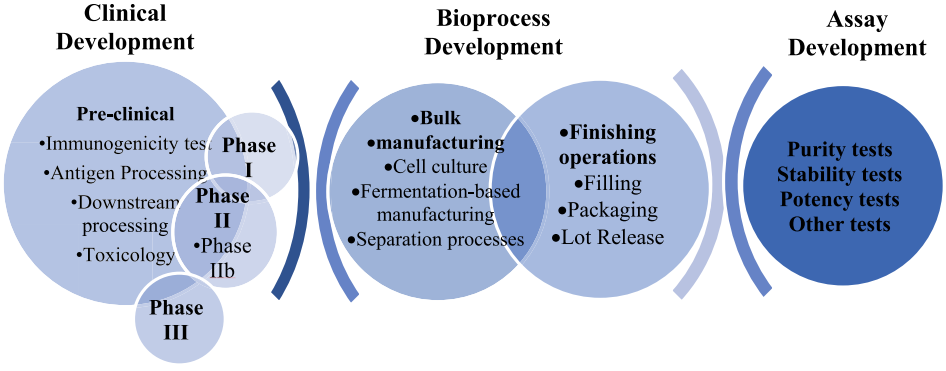

Fig. 1. Process of vaccine development. Adapted from various sources; including Plotkin, Orenstein, and Offit (2013), H. L. Levine (2010); and Technology Transfer Initiative, WHO. Note: In some instances, vaccine manufacturers establish bulk manufacturing construction prior to Phase III clinical trials but after Phase I and Phase II clinical trials show promising results.

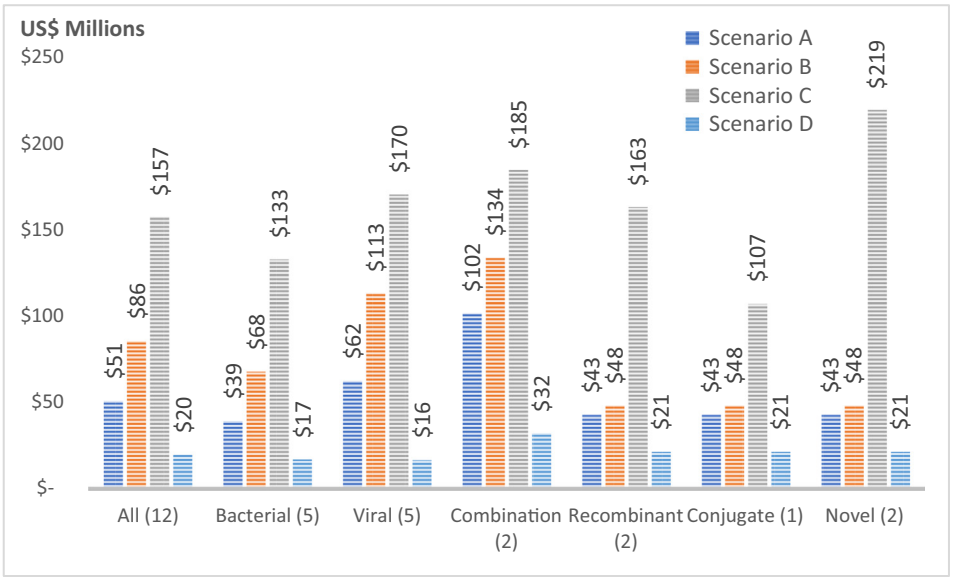

Fig. 2. Calculations of fixed costs for vaccine facilities in developing countries, based on four hypothetical scenarios. Scenario A: 20 million annual doses – 1 vaccine (greenfield); Scenario B: 20 million annual doses – 5 vaccines (greenfield); Scenario C: 100 million annual doses – 5 vaccines (greenfield); Scenario D: 100 million annual doses – 1 vaccine (brownfield).

the average failure rates associated with such a development, to estimate the full economic cost of production.

2.3. Variable costs

For variable costs, respondents were asked to provide two different variable costs, relevant to downstream processes. The first question asked for the cost of goods required for vaccine manufacturing, estimated per bulk dose released. These costs only included running costs such as labour, materials, and maintenance, with no account of R&D, buildings, or equipment. In the second question, respondents were asked to provide estimates of the costs of filling. These were comprised of costs of vials or syringes, stoppers, labels, QC, and release.

Given the variability of vaccine formulation presentations, respondents were also asked to identify costs based on four common vaccine presentations, these are: multi-dose vial (in this case a 10-vial dose), single-dose vials, pre-filled syringes, and a lyophilised (or freeze dried) dose.

2.4. Comparison to vaccine market prices

To assess how the estimated costs generated in this analysis would perform in both developing country and industrialized country markets, a comparison was made with market prices of vaccines in both markets. Vaccine market price data were obtained from a WHO database for the Vaccine Product, Price, and Procurement (V3P) project [13]. These data, reported by countries, included prices of vaccines procured by low, middle, and high-income countries over 10 years (2005–2015). For the purpose of this analysis, the market price data used were for 2014 and adjusted to 2018 using a consumer price index (CPI) method. The data included prices for 48 vaccine types, produced by 31 vaccine manufactures, procured and reported by 41 different countries.

Comparison to market prices allows an observation of producer surplus which is an economic concept that measures the difference between the amount a producer receives and the minimum payment it is willing to accept. This difference represents the benefit that the producer receives for the good or service it sells in the market [14]. An analysis of producer surplus was also presented by Herlihy et al. [4].

To have a comparable analysis, the price data from the V3P database were aggregated by similar cost drivers applied to the questionnaire data. These were: vaccine formulation presentations (i.e.: multi-dose, single-dose, prefilled syringe, and lyophilised) and vaccine technology types (i.e.: all, bacterial, viral, combination, recombinant, and conjugate vaccines). The vaccine price data included additional estimates for vaccines using lyophilised with pre-filled formulations, which will be presented though not compared to the cost data because costs were not available for this vaccine type.

2.5. Economic benefit of fill finish mechanisms versus procuring finished vaccines

In addition to cost estimations, respondents were asked to assess, based on their experiences, the economic benefit, in particular the cost savings of procuring antigens as bulk doses in comparison to procuring finished vaccines for both traditional and modern vaccines. This economic benefit was estimated by the differences reported between the two procurement methods, by different vaccine technologies (traditional and modern vaccines) and production scale (1–5 million doses and 10–20 million doses) (see question number 10 in the Appendix).

2.6. Analysis

The assumptions used in the analysis were adopted from studies by Mahoney [5]; Mahoney, et al. [6] and Mercer Managment Consulting [15,16]. The analysis in this paper however included opportunity costs, by incorporating the cost of failure rates and an annualization factor. This is to ensure that the total economic costs of production were accounted for and represented in the vaccine costs-per-dose estimations. Life-year assumptions were applied to each fixed and semi-fixed cost component: buildings, equipment, and validation batches. These assumptions were adopted from Mahoney, et al. [6] as follows: buildings and equipment were assumed to have 25 and 10 year lifespans respectively. For semi-fixed costs of validation batch production, the analysis

used the lifespan applied to equipment (10 years) with the assumption that validation batches are required when a new piece of equipment and/or facility is used.

The annualised fixed cost-per-dose was calculated by adopting the following formula [17,18]:

$$C_a = (V - R)\mathrm{a} \quad (1)$$

where C_a is the annualised capital cost of equipment, obtained by multiplying the acquisition cost of the equipment V, after deducting its estimated residual value R, by an annualization factor a.

Further, the annualization factor was calculated as follows:

$$a = \frac{r(1+r)^n}{(1+r)^n - 1} \quad (2)$$

where r is the annual interest rate and n is the life of the equipment (in years) and the residual value R is assumed to be zero. The discount rate used for capital costs was were assumed to be 5% with reference to Clendinen, et al. [2]. A sensitivity analysis was performed using a 10% discount rate. As for life years of buildings and equipment, the assumption used by Clendinen, et al. [2] as well as Mahoney, et al. [6] was adopted and fixed costs were assumed to be made up of two-thirds of facility costs and one-third of equipment costs [19]. These were then divided by the total number of doses produced in each production setting.

As in Mahoney [5], the estimates were summarised as follows:

- *Raw Materials & Direct Labour* equalled the fill and finish costs;
- *Assay Costs* equalled the bulk-dose release costs;
- *Indirect costs* equalled 15% of the total of the two costs above as factory overhead, plus 5% of the same total for administrative overheads;
- *Depreciation* was the annualised capital cost-per-dose; and
- *Total cost-per-dose* was the sum of all of the above.

The analysis did not differentiate between bulk doses produced in-house and those that were imported. The currency of analysis was US dollars. Where a different currency was provided in the questionnaire response, an exchange rate at the time of data collection was used, based on the official UN converter (https://treasury.un.org/operationalrates/OperationalRates.php).

3. Results

3.1. Cost structures

On average, fixed costs based on the twelve observed vaccines were US$ 50.8 million, US$ 85.6 million and US$ 157.4 million for Scenarios A, B, and C respectively. Further, the average estimate provided for Scenario D was US$ 19.6 million (Fig. 2).

All of the responses indicated that as production scale and scope increased, fixed costs in vaccine production have a step-cost pattern, where higher fixed costs are required when current production surpasses a certain threshold. Further, the average increase in fixed costs between Scenario A and Scenario B (US$ 51 million to US$ 86 million) and between Scenario B and Scenario C (US$ 86 million to US$ 157 million) where the increase in production is five-fold under both scenarios, indicated increases of 69% and 83% in fixed costs respectively.

R&D costs in bringing a vaccine to market were estimated to be an average of US$ 18.1 million, with vaccine type-specific estimates of between US$ 8.0 million (combination vaccines) and US $ 85.6 million (novel vaccines). One respondent provided an estimated figure ranging between US$ 500 million to US$ 1 billion, however as this was assumed to be taken from existing literature [20,21], rather than being an original observation, this estimate was excluded from the analysis. While research in this area has often produced R&D costs of US$ 500 million to US$ 1 billion and higher, these results are averages across all therapeutic areas, firm sizes and types of molecule (traditional chemical compound or biologic) and R&D costs of vaccines are known to be substantially lower on average than other new molecular entities [21–23].

The respondents estimated the success rates to be an average of 75%, ranging from 55% (novel vaccines) to 98% (combination vaccines). This was inversely correlated with the R&D costs reported above. The novel vaccines included in this analysis, which showed the lowest success rates, were produced under technology-transfer arrangements.

The annualised capital costs were on average US$ 0.34, US$ 0.10 and US$ 0.035 per dose across scenarios A, B, and C respectively. Capital costs-per-dose were found to be lower as production scale and scope increased.

The average variable costs-per-dose were US$ 1.89 for a one million dose production, and US$ 1.87 and US$ 1.23 respectively for 20 million and 100 million dose productions.

The overall average costs-per-dose were found to be US$ 2.41 (Scenario A), US$ 2.18 (Scenario B), and US$ 1.96 (Scenario C). The costs lowered as production scale and scope increased (from Scenario A–C). This was also consistent across both observed cost drivers: vaccine technology types and formulation presentation (Fig. 3).

3.2. Cost patterns

The results show that economies of scale and economies of scope were both present across all vaccines observed; and on average, the economies of scope were similar to the economies of scale (9.7% versus 9.8%). Further, the economies of scope had a smaller range (6.7–19.3%) than economies of scale (2.4–20.7%). With the exception of recombinant vaccines, prefilled syringe and lyophilised vaccines, the economies of scope were either similar or greater than economies of scale for the different vaccine technology types and formulation presentations (Fig. 4).

A sensitivity analysis was performed using a discount rate of 10% instead of 5% in annualizing capital costs. The results were similar in that economies of scale and scope were also present across the different vaccine technologies and formulations observed. However, there was not any significant difference in the percent market share for domestic markets or the global and export markets.

3.3. Market price comparisons

Fig. 5 shows the comparison between costs-per-dose in Scenarios A, B, and C and the price-per-dose of vaccines, within the industrialized-country and developing country markets. For the industrialized country markets, the costs-per-dose estimated from the analysis were on average 84% lower than the vaccine price-per-doses reported being procured in industrialized vaccine markets. This suggests there is potential for gaining producer surplus in this particular market.

While for developing-country markets, the overall average costs-per-dose was 47% lower than the vaccine prices-per-dose in developing-country markets. Vaccine categories where the reported prices were lower than the estimated costs were recombinant vaccines, multi-dose vaccines, and (only slightly) lyophilised vaccines.

3.4. Economic benefit of fill finish mechanisms versus procuring finished vaccines

Six of the eight responding manufacturers provided answers to the question indicating the economic benefits, in particular cost

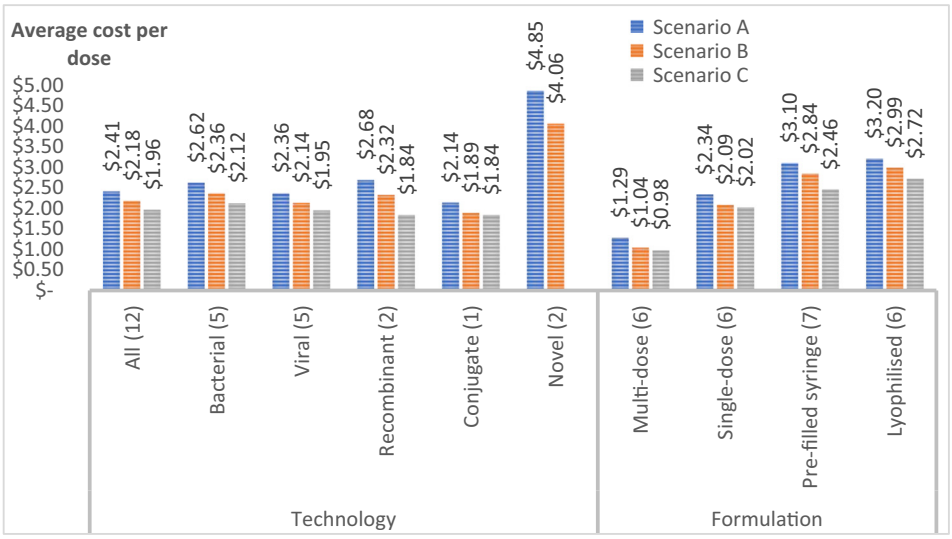

Fig. 3. Estimations of average cost-per-dose for vaccines produced in developing countries. Data based on 12 vaccine examples provided by eight DCVMs. Estimations based on three hypothetical scenarios. Scenario A: 20 million annual doses – 1 vaccine; Scenario B: 20 million annual doses – 5 vaccines; Scenario C: 100 million annual doses – 5 vaccines.

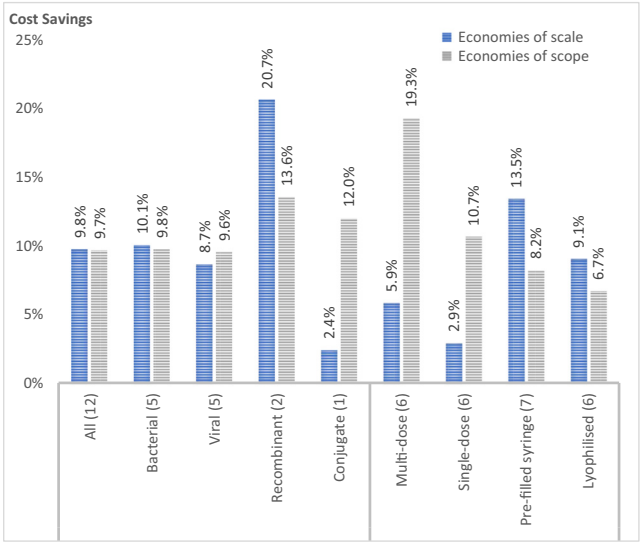

Fig. 4. Estimations of economies of scale and economies of scope for costs-per-dose of vaccines produced in developing countries. A1: Economies of scale; B1: Economies of scope. Data based on three hypothetical scenarios. Scenario A: 20 million annual doses – 1 vaccine; Scenario B: 20 million annual doses – 5 vaccines; Scenario C: 100 million annual doses – 5 vaccines.

savings of vaccines procured as a finished product as opposed to establishing a fill and finish mechanism for bulk material, as shown in Fig. 6. Overall, the economic benefit was reported to be higher when vaccines are procured as antigen and filled locally, for high volume procurement and in modern vaccines.

4. Discussion

The study found that the overall average cost-per-dose of producing vaccines in developing countries was US$2.18, with a range between US$ 0.98 (Scenario C for multi-dose vaccines) and US$ 4.85 (Scenario A for novel vaccines). These estimates are in agreement with reported costs of vaccines produced by multinationals [15], which suggested costs ranging between US$ 0.05 to US$ 3–US$ 4 per dose. The vaccine markets faced by DCVMs however are mostly non-premium markets. WHO reports that vaccine markets in low and middle-income countries contribute to only 18% of the total market value of vaccines [24], yet this may be compensated by other features found in developing country vaccine markets, such as the large size of the population and the high need for vaccines due to disease burden profiles. WHO reports that 85% of the world's population live in low and middle-income countries, while 93% of the burden of disease is found in these countries [24].

The study also suggests that, at an annual production of 20 million doses of one vaccine, increasing the scale and scope of production will result in a lower cost-per-dose. Cost-per-dose, though mainly driven by fixed costs as mentioned in Luter, et al. [25], becomes driven by variable costs at production scales over 20 million doses. This is an advance on the current literature because other vaccine cost studies have focused mainly on the contributions of fixed costs.

An interesting finding was that the fixed costs required across the different scenarios suggest a pattern of step fixed costs in establishing new vaccine manufacturing facilities in developing countries, whereby, upon passing a certain production threshold (i.e.: from single to multiple vaccine facilities, or production scales of 20 million doses to 100 million doses, or the combination of these), a higher fixed cost is required. The presence of this step cost feature emphasises the importance of demand forecasting for vaccine manufacturers. This step cost feature however also implies that the cost estimates generated in this study may not be applicable to production scale and scope settings that are different from the ones used in the analysis.

The failure rate of developing country manufacturers was found to be an average of approximately 25%, with a range of 3–55%. This range was significantly lower than what was found by Pronker et al. who found a wide variety of figures across different studies, ranging from 7% to 78%. Their study however covered originating vaccines or new chemical entities where success rates are notoriously low [22]. The low failure rates as well as the low R&D costs found in this study were not entirely surprising given that vaccines produced by developing country manufacturers are mostly developed through technology transfer arrangements that have passed some if not all of the development and clinical testing stages.

Under the three hypothetical scenarios used to analyse and compare respondents, costs-per-dose of vaccines produced by

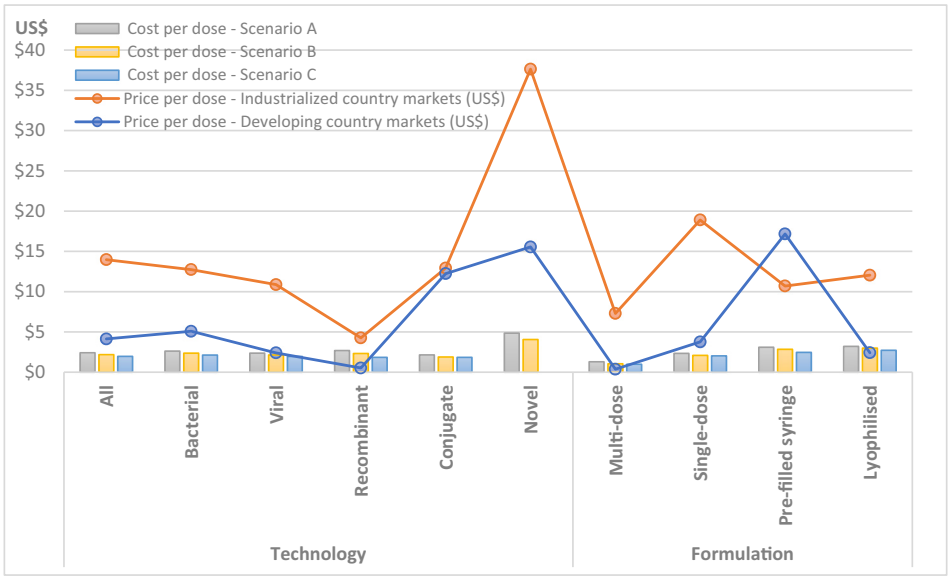

Fig. 5. A comparison of estimated developing country vaccines' costs-per-dose based on hypothetical Scenarios A, B, and C to prices-per-dose paid by industrialized and developing countries. Costs based on scenarios: Scenario A: 20 million annual doses – 1 vaccine; Scenario B: 20 million annual doses – 5 vaccines; Scenario C: 100 million annual doses – 5 vaccines; Price data for industrialized countries from V3P database, WHO (2018).

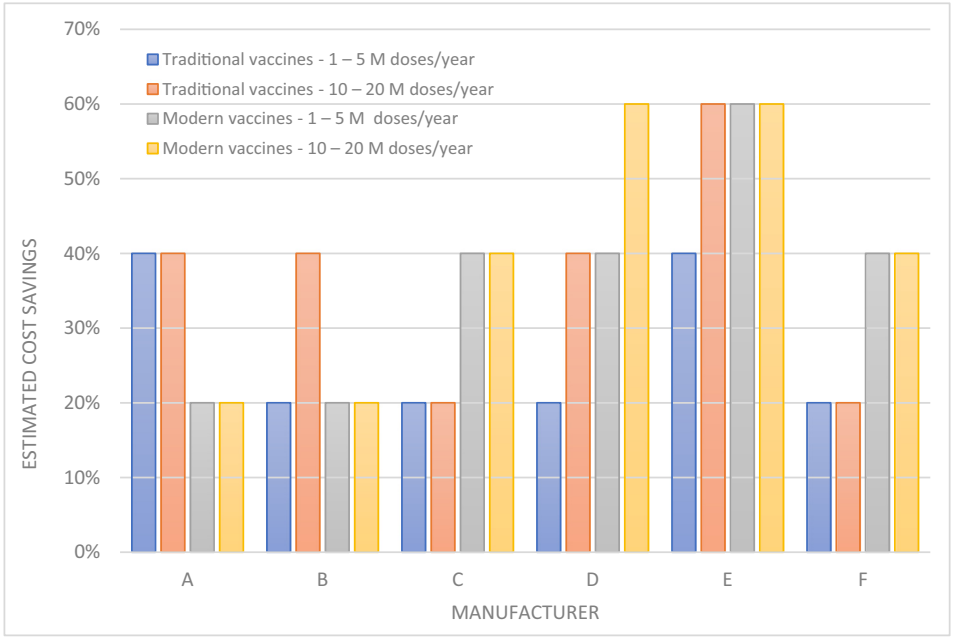

Fig. 6. Estimated economic benefit/cost savings from procuring antigens and filling compared to procuring finished vaccines, for traditional vs modern vaccines, by production scale. Data based on six DCVMs, e.g.: if procuring finished vaccine costs US$ 10 for a vial but fill-finish vaccine costs US$ 4 (US$ 3 for bulk purchase + US$1 for filling) the benefit would be 60%.

developing countries were on average 47% lower than vaccine prices in developing country markets and 84% lower than prices in industrialized country markets. In developing country markets, local producers would gain most producer surplus in bacterial, and conjugate technology type vaccines and in pre-filled syringe formulations. With regards to industrialized country markets, these manufacturers have the potential to gain higher producer surplus when producing conjugate and novel technology vaccines as well as in multi-dose and single-dose vaccine formulations. For local vaccine producers to access industrialized country markets however, they must be prepared to consider a portfolio that reflects the market divergence of developing and industrialized countries [26–28] as well as different regulatory requirements in industrialized countries [25].

The findings also suggested that an estimated 9.7–9.8% of cost savings through economies of scope and scale can potentially be achieved by increasing the scope and scale of production facilities, regardless of vaccine type. If the vaccine is recombinant, economies of scale can be twice as high. Little variation in economies of scope was found based on formulation presentations, except for multi-dose types (19.3%).

A number of constraints were faced in generating the data. Ideally, direct observation would be made, where disaggregate cost estimates are generated based on each respondents' actual vaccine

production scale and scope. However, such an approach may not easily generate a large number of respondents or case studies due to the sensitivity of commercial cost data. Further, given the structural differences in cost accounting methods across companies and countries, cost estimates may not necessarily be comparable across different countries or manufacturers. An additional limitation was that a direct comparison between greenfield and brownfield production was not possible because Scenario D did not have the same production scale and scope as the baseline greenfield scenarios (Scenarios A, B or C). Direct comparison of brownfield and greenfield production is a recommended area of future research. To avoid any confusion, the inclusion of utilities included in the fixed cost component refers to water treatment (where treatment facility may be required) and electricity where a powerhouse may need to be built. This was also noted in Sinclair, et al. [29].

In conclusion, DCVMs can produce vaccines that are affordable when production is made at a scale that is over 20 million annual doses. For this, manufacturers should ideally have facilities that produce multiple vaccines.

Conflict of interest

None

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Appendix A. Supplementary material

Questionnaire on the cost structure of vaccine production in developing countries. Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.050.

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