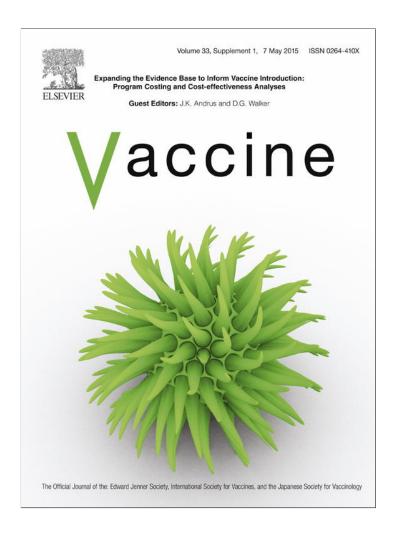
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The drivers of facility-based immunization performance and costs. An application to Moldova



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ABSTRACT

Objective: This paper identifies factors that affect the cost and performance of the routine immunization program in Moldova through an analysis of facility-based data collected as part of a multi-country costing and financing study of routine immunization (EPIC).

Methods: A nationally representative sample of health care facilities (50) was selected through multistage, stratified random sampling. Data on inputs, unit prices and facility outputs were collected during October 3rd 2012–January 14th 2013 using a pre-tested structured questionnaire. Ordinary least square (OLS) regression analysis was performed to determine factors affecting facility outputs (number of doses administered and fully immunized children) and explaining variation in total facility costs.

Results: The study found that the number of working hours, vaccine wastage rates, and whether or not a doctor worked at a facility (among other factors) were positively and significantly associated with output levels. In addition, the level of output, price of inputs and share of the population with university education were significantly associated with higher facility costs. A 1% increase in fully immunized child would increase total cost by 0.7%.

Conclusions: Few costing studies of primary health care services in developing countries evaluate the drivers of performance and cost. This exercise attempted to fill this knowledge gap and helped to identify organizational and managerial factors at a primary care district and national level that could be addressed by improved program management aimed at improved performance.

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1. Introduction

Cost-effectiveness of immunization programs is well documented worldwide within developed and developing country settings [1–5]. Although strong steps have been taken globally to expand immunization coverage rates, the progress is not sufficient in many countries and several issues are still pending on the international agenda: how to identify and reach out to nonserved population? Which new vaccines need to be considered in an improved vaccination calendar? What are the costs of including them (both non-served population and new vaccines) in the current immunization plans?

As in many other health care services, strategies of immunization programs and their cost structures cannot be replicated from one country to another. Population density, their location and accessibility along a territory, distribution of health care services

* Corresponding author. Tel.: +54 11 4861 2126. E-mail address: danielmaceira@cedes.org (D. Maceira). and population characteristics (health habits and education) all have strong influence on costs of delivering vaccination services [6,7]. Vaccine procurement mechanisms, status of cold chain and managerial capacity also influence success of vaccination initiatives. Global evidence on what determines cost of immunization and how much is necessary for developing countries to deliver these services is still inconclusive. Our study aims at contributing additional evidence around the topic of immunization costs and productivity determinants, by using the facility level costing data from Moldova.

Particular studies on cost determinants for immunization programs provide rich insights about relevance of particular factors under specific scenarios. Bishai et al. [8] analyzes average costs and DTP3 coverage, by using a fifty-country panel data from 2000 to 2003 arising from WHO and GAVI sources. They prove the presence of strong economies of scale in the provision of immunization coverage. Also using facility data, Robertson et al. [9] calculated average costs per Fully Immunized Child (FIC) in Gambia, which further contributed to the argument of decreasing costs with scale. In the same direction, Kahn et al. [10] based on immunization centers in Dhaka,

Table 1Summary statistics, unweighted sample.

Variables	Obs.	Mean	Std. Dev.	Min.	Max.
Fully immunized child (FIC)	50	60.88	135.16	1	714
Total number of doses administered	50	895.20	1844.43	33	9060
Total economic cost, facility level	50	11,942	21,743	565	112,548
Total economic cost, facility + district level	50	12,502.23	22,404.94	627.75	115,062
Total economic cost, facility + district + national level	50	12,663.11	22,723.92	641.27	116,657
Share of staff time spent in the facility for immunization in % (FTE)	50	1.32	2.01	0.2	10.20
Total working hours	50	51.22	12.12	8	71
Total facility square meters	50	577.76	1173.18	20	5820
Cold chain capital index (cold chain economic cost at facility level, in USD)	50	72.86	22.20	7.79	136.14
Hourly wage, mid career nurse (USD)	50	1.82	0.16	1.45	2.28
Refrigerator unit price (USD)	50	0.76	0.36	0.01	2.13
Total number of infants in the facility catchment area	50	66.06	149.98	1	810
Share of population with university education in %	50	6.46	5.38	2.90	24.40
Dummy facility type (=1 if FMC)	50	0.10	0	0	1
Dummy doctor at the facility (=1 Yes)	50	0.88	0.33	0	1
Dummy facility location (=1 if Urban)	50	0.06	0.24	0	1
Distance from the facility to the vaccine collection point	50	19.60	13.14	0	50
Overall wastage rate in $\overset{\leftarrow}{x}$ (from total number of doses administered)	50	17.01	8.89	4.90	36.90

Bangladesh, calculated average cost of FIC during the year 1999. Results prove decreasing costs with population scale, and identified the relevance of community support in reaching higher coverage.

Creese et al. [11] looked at costs per FIC in Indonesia, Philippines and Thailand, analyzing 1978/79 facility level data. Bi-variate analysis across institutions and countries found significant rural-urban differences in input prices as well as in population accessibility to the services. Walker et al. [12] looked at disaggregated immunization costs per budgetary line in three Peruvian districts and calculated average expenses per FIC. Findings show significant differences across urban and rural locations, as well as among types of facilities, suggesting the presence of geographical access barriers in reaching with immunization.

Particular goal of this paper is to identify production and costs determinants on a facility level as well as on a district and national level. Understanding productivity and cost determinants will help in identifying key arguments to improve allocative efficiency in resources utilization looking for reaching the still non-reached population. Are input prices relevant to determine immunization cost structures? Are facility types a relevant factor in the design of a vaccination campaign? What is the relevance of scale (number of children to be immunized) at the moment of selecting the immunization activity plan? Ordinary least square (OLS) method was

applied to a traditional cost function structure, recognizing a multivariate influence of different factors on Moldovan immunization costs, where production variables as well as population and health system characteristics participate in the definition of total costs, at the facility, district and national levels.

2. Methods

Out of 1318 health care facilities delivering immunization services in Moldova across 37 districts, the research team sampled 50 institutions, combining districts with urban and rural locations, as well as capturing diversity of health service providers, more details on sampling are described elsewhere [13]. Details about costs and cost elements are also available from the full study report [14].

The survey allowed capturing facility performance indicators (fully immunized child and number of total doses administered), human resource characteristics and their participation in the immunization activity (hours worked on immunization activities, presence of doctor in the health center), as well as a facility specific scale factors (total square meters per facility, cold chain).

Beyond this information, the facility-based dataset was enriched with data about input prices, and socio-economic characteristics (number of infants in a catchment area, average household income, education level of families, etc.).

Table 1 summarizes descriptive statistics for un-weighted sample of facilities. (See Table 5 in the Annex for a glossary of variables).

The estimation strategy considers a sequence of two steps. The first step analyzes determinants of main production indicators/outputs: what explains the number of FIC and the total number of doses administered on a facility level? In order to

¹ Facility level costs include only facility specific cost and do not take into account costs incurred outside the facility such as costs of district and national public health centers; district level costs comprised by the facility specific costs and costs of district public health centers that were allocated down to a facility level and the national level costs consist of facility, district and national costs.

answer these questions, we looked at variables related to inputs: human resources and facility capacity/specification, corrected by scale variables (number of infants in catchment area), as well as by wastage rates, seen as a proxy for a facility management practices.

Applying a linear production function, immunization outputs take the form:

$$Q_{.}i = A_{.}i + \alpha_{.}1 \times L_{.}i + \alpha_{.}2 \times K_{.}i - \alpha_{.}3 \times W_{.}i$$

$$\tag{1}$$

where, Q is the output indicator (FIC or number of doses administered) for facility i, L (labor) and K (capital) are production factors, with participation $\alpha 1$ and $\alpha 2$ respectively, and A is the scale of infants present in the catchment area. The production function also depends on the wastage rate (W), which weighted the productivity of each factor.

Applying natural logarithms on the left side of the equation (1) facilitates the use of ordinary least square estimations techniques and the calculus of semi-elasticities in production with respect to a relevant input indicator(s). They allow identifying how output production changes (in percentages) when input each factor is modified by one unit (keeping constant all other factors)^{2–3}:

$$\ln Q \cdot i = A \cdot i + \alpha \cdot 1 \times L \cdot i + \alpha \cdot 2 \times K \cdot i + \alpha \cdot 3 \times W \cdot i$$
 (2)

The second estimation step proposes to answer: what determines the cost of immunization services? For this purposes we use the Total Economic Cost at a facility level as well as at district and national levels as dependent variables.

The costs model implemented is based on a traditional cost structure $CQ_{..}i=w_{..}i.K.i+r_{..}i.L.i$, expressed in natural logs, adding contributions from the literature on hybrid costs models, where prices, quality-driver and demand side characteristics interact [15,16], in the form:

$$\ln CQ_{-}i = \ln FIC_{-}i + \alpha_{-}1\ln w_{-}i + \alpha_{-}2\ln r_{-}i + \alpha_{-}3\ln W_{-}i + \alpha_{-}4\ln P_{-}i$$
 (3)

where, CQ is the total economic cost for the facility i (i = 1...50), w and r are input prices for labor force and infrastructure (as it will be detailed in the next section), FIC captures the effect of the size of the objective population (scale factor) which incorporates the level of inputs involved. 4 W is a proxy of managerial quality (wastage rate) and P introduces the relevance of demand-side variable in the cost structure (i.e. education and income of the population affected by the program).

3. Results and discussion

3.1. First step: production determinants

We proposed two production indicators following the specification in equation (2): "Number of Fully Immunized Children" and "Total Number of Doses Administered" per facility. Although both dependent variables relate to the service production capacity of a facility, the "Number of Fully Immunized Children" involves a quality dimension (it requires children identification, on-time follow-up, etc.).

As fixed facilities – with no outreach activities – are responsible for explaining immunization performance in Moldova, explanatory variables used in the regression are related to health center characteristics: facility level inputs (human resources and infrastructure), proxy variables explaining logistics required for vaccine distribution i.e. distance to vaccine collection site, size of population in a facility catchment area and facility type. In addition, the variable "wastage rate" was included as proxy for managerial effectiveness at the provider level.⁵

Table 2 presents the results of this regression. Firstly, human resources are positive and significant related at 1% level on facility outputs, with similar magnitude and relevance in all specifications.⁶ Furthermore, two alternative measures of capital were included: facility square meters and the cold chain capital index,⁷ intending both to capture productivity issues related to infrastructure. In the case of total number of doses administered, coefficients of both variables show to be significant at 5% level, although their effects on productivity are smaller than those of human resources. Cold chain capital index does not affect FIC but has positive and statistically significant association on the total doses delivered, and its relevance is greater that of square meters.

The number of infants in a catchment population, show to have positive relationship in explaining higher immunization outputs, but its magnitude is lower when their coefficients are compared with those which relates to human resources.

The distance to vaccine collection site and type of medical facility do not have statistically significant influence on productivity. On the other hand, the presence of doctors in the facility has strongest influence on the number of doses delivered and number of FICs produced. All specifications show to be statistically significant at 1% level.⁸

Finally, wastage rate have negative coefficients on both output indicators, statistically significant at 1% level, although with slightly stronger implications for the total number of doses administered.

Beyond the predictive capacity of the model implemented, the obtained R2 might be also the result of the small size of the sample available to pursue the analysis. The same consideration applies to the results reached at the second estimation step.

3.2. Second step: cost determinants

For evaluating determinants of costs we used Eq. (3) described earlier, with two alternative approaches. The first approach used facility-specific scale and input prices variables—specifications (1) through (4) in Table 3, reflecting prices of identified main labor and capital inputs used in vaccination activities, such as hourly USD wages for mid career nurses, unit USD prices for ice packs

² Originally, a Cobb-Douglas functional form was considered as a potential specification for the production function, given its relative straightforward reading of coefficients within a log linear equation. However, it assumes constant elasticity of substitution, which imposes a constraint to the estimation. In addition, histograms of both dependent variables used in the econometric implementation (fully immunized children and total number of doses administered) suggest the presence of a semi-log specification. For more details see [14].

³ Although Poisson and Negative Binomial estimation forms are useful in studying health care related issues (visits to doctors, number of inpatient days, etc.), in our case the dependent variables do not fit into those alternatives: although integer and positive, observations are not concentrated on values 0, 1, 2, etc., and there are not zero values involved (see Table 1 in the paper).

⁴ A production function shows the technological relation of inputs to produce a good or service (immunized children, in this case), while cost function is triggered by input prices, given a technological production structure. As the former is an antecedent of the latter, the econometrical implementation instruments a two-step estimation, where the result of the first step is incorporated in the second.

⁵ Breusch-Pagan/Cook-Weisberg tests were performed to detect any linear form of heteroscedasticity. Additionally, estimations use robust standard errors to deal with this potential specification problem (Manning and Mullahy [1]).

⁶ Nevertheless, the analysis may involve potential issues related to endogeneity. The share of staff time spent on immunization affects the number of fully immunized children that does not reveal that it is possible that health care personnel are responding to demand requirements.

One possible measure of capital in immunization activities is cold chain capacity at the health center. As these devices varies in capacity across facilities, one potential way of capturing the scale of this factor is to use its total costs at the facility, under the assumption that capacity and costs are related.

⁸ The facilities studied do not show the presence of correlation between experience (seniority) of the nurses participating in the vaccination team and immunization performance.

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Table 2 Determinants of production.

	Ln FIC			Ln total dose adm.			
Variables	(1)	(2)	(3)	(4)	(5)	(6)	
Total working hours	0.0311** (0.0121)	0.0330*** (0.0114)	0.0315*** (0.0114)	0.0249*** (0.0087)	0.0269*** (0.0074)	0.0254*** (0.00728)	
Total facility square meters	0.000507** (0.000219)		0.000461** (0.000218)	0.000523** (0.00021)		0.000459** (0.000204)	
Cold chain capital index		0.0109 (0.00717)	0.00955 (0.00705)		0.0147** (0.00575)	0.0133** (0.00555)	
Total number of infants	0.00636***	0.00577**	0.00547**	0.00538***	0.00444^{*}	0.00413**	
in the facility catchment area	(0.00213)	(0.00273)	(0.00219)	(0.00173)	(0.0023)	(0.00172)	
Dummy facility type (=1 if FMC)	-1.708 (1.123)	-0.0152 (1.04)	-1.62 (1.152)	-1.529 (0.944)	0.192 (0.884)	-1.407 (0.968)	
Dummy doctor at the facility (=1 Yes)	0.585*** (0.209)	0.676*** (0.239)	0.627** (0.235)	0.702*** (0.213)	0.809*** (0.219)	0.760*** (0.22)	
Distance from the	0.0036	0.00553	0.00583	-0.000313	0.0025	0.0028	
facility to the vaccine collection point	(0.00882)	(0.00947)	(0.00926)	(0.00655)	(0.0071)	(0.00669)	
Overall wastage rate	-0.0387*** (0.0105)	-0.0399*** (0.0101)	-0.0402*** (0.00963)	-0.0460*** (0.0101)	-0.0478*** (0.00969)	-0.0481*** (0.00899)	
Constant	0.703 (0.823)	-0.119 (1.147)	0.0121 (1.135)	3.982*** (0.663)	2.888*** (0.796)	3.018*** (0.779)	
R-squared	0.721	0.714	0.735	0.779	0.787	0.811	

Notes: Robust standard errors in parentheses. Significance levels:

Table 3 Determinants of total economic cost, facility level.

Dep. var.: In total economic cost, facility level								
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Ln Fully Immunized Children (FIC)	0.743*** (0.0598)		0.743*** (0.0548)		0.615*** (0.0749)		0.616*** (0.164)	
Ln FIC est.		0.815*** (0.107)		0.813*** (0.109)		0.694*** (0.150)		1.720*** (0.218)
Ln FIC2							-0.000218 (0.0297)	
Ln FIC2 est.								-0.139*** (0.027)
Ln hourly wage, mid career nurse	1.122 (0.981)	1.442** (0.532)	0.991 (1.024)	1.409** (0.569)	1.050 (0.986)	1.395** (0.593)	1.050 (0.999)	1.628* (0.619)
Ln refrigerator unit price	0.0502 (0.0823)	0.183*** (0.0361)	-0.0745 (0.165)	0.152 (0.133)	-0.0651 (0.137)	0.132 (0.133)	-0.0651 (0.139)	0.132 (0.112)
Ln ice pack unit price			-1.033 (1.127)	-0.261 (1.086)	-1.468 (0.947)	-0.667 (1.111)	-1.469 (1.007)	-0.934 (0.904)
Ln share of population with university					0.618***	0.447*	0.619**	0.692***
education					(0.186)	(0.229)	(0.264)	(0.174)
Ln overall wastage rate					-0.00933 (0.175)	-0.0188 (0.200)	-0.00945 (0.181)	0.210 (0.156)
Constant	5.526*** (0.661)	5.303*** (0.512)	2.649 (3.309)	4.581 (2.993)	0.842 (2.924)	3.130 (3.279)	0.837 (3.187)	-0.283 -2.839
R-squared	0.815	0.795	0.821	0.795	0.859	0.811	0.859	0.891

Notes: Robust standard errors in parentheses. Significance levels: p < 0.1. p < 0.05. p < 0.01.

^{*} p < 0.1. ** p < 0.05. *** p < 0.01.

Table 4Determinants of total economic cost, facility + district, and facility + district + national level.

Dep. var.: In total economic cost									
	Facility + district level				Facility + district + national level				
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	
Ln fully immunized children (FIC)	0.749*** (0.0525)		0.609*** (0.160)		0.750*** (0.0522)		0.608*** (0.159)		
Ln FIC est.		0.818*** (0.106)		1.719*** (0.204)		0.819*** (0.105)		1.717*** (0.202)	
Ln FIC2			0.00274 (0.0286)				0.00329 (0.0284)		
Ln FIC2 est.				-0.138*** (0.0255)				-0.137*** (0.0252)	
Ln hourly wage, mid career nurse	0.919 (0.989)	1.339** (0.553)	0.979 (0.964)	1.561** (0.610)	0.91 (0.981)	1.331** (0.551)	0.971 (0.956)	1.553** (0.608)	
Ln refrigerator unit price	-0.0612 (0.155)	0.167 (0.127)	-0.0490 (0.132)	0.151 (0.106)	-0.0597 (0.154)	0.169 (0.127)	-0.0471 (0.131)	0.153 (0.105)	
Ln ice pack unit price	-0.973 (1.075)	-0.197 (1.049)	-1.355 (0.958)	-0.817 (0.870)	-0.967 (1.067)	-0.19 (1.045)	-1.342 (0.951)	-0.804 (0.866)	
Ln share of pop'n with university education			0.579** (0.256)	0.661*** (0.168)			0.574** (0.254)	0.658*** (0.167)	
Ln overall wastage rate			-0.0205 (0.182)	0.195 (0.150)			-0.0216 (0.182)	0.193 (0.149)	
Constant	2.914 (3.151)	4.859 (2.886)	1.350 (3.048)	0.234 (2.723)	2.944 (3.127)	4.893* (2.873)	1.413 (3.025)	0.302 (2.707)	
R-squared	0.835	0.806	0.869	0.899	0.838	0.808	0.871	0.900	

Notes: Robust standard errors in parentheses. Significance levels:

and refrigerators, for which data is present and available across all facilities ⁹

In the second approach, in addition to price variables, hybrid specifications were considered, by adding two variables—specifications (5) to (8) in Table 3. The first one relates to a facility management practice associated to efficiency in the use of resources (wastage rates). The second variable accounts for demand-side factors – characteristics of households – (income, educational level, etc.), which may affect demand for health services [17,18]. As potential demand side variables were strongly cross-correlated, we only retained the share of population with university education.

In both cases, the scale factor is the total number of FIC (or FIC estimated). ¹⁰ Based on the available evidence, the expectation is that higher scale will require more resources to deliver immunization services and therefore the total facility costs will be higher. However, due to economies of scale, we also expect cost per FIC to decline as the scale increases. The variable FIC² (the square of FIC) – if its coefficient is negative and statistically significant – will support that hypothesis.

Results are presented in Table 3. Specifications (1), (3), (5) and (7) show FIC coefficients to be positive and significant at 1% level. Using natural logs in both sides allows identifying product elasticities: 1% change in FIC is related to 0.615–0.743% change in total

Prices of human resources and capital do not show conclusive and strong relevance on the total cost of immunization. ¹¹ Only labor prices – as well as refrigerator prices – reveal statistically significant association when FIC-estimated is used in the regression. On the other hand, ice pack unit prices are not significant under any specification of the model.

Columns (5) to (8) in Table 3 introduce supply and demand characteristics, in addition to input prices. ¹² Demand-side variables show their explanatory power (positive and significant at 1% level) over immunization costs on a facility level under any specification. A possible interpretation is that educated people demand higher quality and more services, which is associated with greater cost, as prices coefficients remain similar across facilities. Wastage rate proved not to have significant influence over costs in any specification.

As Fig. 1 shows, total immunization costs increase with scale (FIC or FIC-estimated). However, the slope of the curve provides an argument about potential decreasing costs as long as the number of FIC increases (i.e., total costs' growth rate is decreasing with scale), as it was pointed in the literature. This effect is captured by

p < 0.1.

^{**} p < 0.05. *** p < 0.01.

immunization costs at the facility level. Replacing FIC for its estimated specification (columns 2, 4, 6 and 8) does not change either the significance or the weight of the variable influence on the total cost, which assures robustness of our findings.

⁹ A detailed analysis of the costs of the Moldovan immunization program is available in a companion paper [13] and in the full research report [14].

¹⁰ As FIC strongly correlates with demand and supply side variables and to avoid multi-collinearity we used FIC estimated as well. The variable is built based on the estimation of FIC arisen from step one of the model. Replacing coefficients obtained in specification (3) of FIC into the original database leads to a new variable, FIC estimated, allowing to link production decisions with the cost structure.

¹¹ The Moldovan remuneration scheme at the public health sector relies on fixed salaries, not adjusted to differences in performance. Therefore, vaccination coverage is not related to the implementation of any specific financing rule based on results.

¹² The approach combines supply and demand characteristics into a single reduced-form regression. Nevertheless, additional information, not available at this stage, may allow estimating a system of equations, in order to capture separately both vectors of determinants.

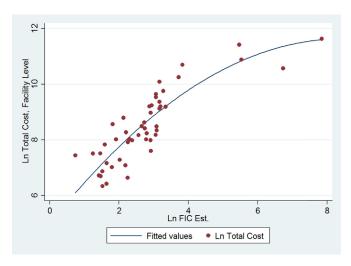


Fig. 1. Total costs by FIC. Estimation at facility level.

introducing variables FIC^2 and FIC^2 -estimated, which are the second power of the scale variables used in our cost estimations, as shown in specifications (7) and (8). The new variable has a negative coefficient and is significant at 1% level when used with the FIC-estimated specification, providing statistical support to Fig. 1. The availability of an increased sample of facilities would provide additional evidence to qualify this finding.

Immunization program in Moldova is strongly centralized. Central Government assumes responsibility for salaries, cold chain, and vaccine and syringe provision as single purchaser, leaving limited responsibility over cost management to lower levels, which are responsible for organizing and managing immunization program locally. Therefore, cost determinants are expected to be mainly dependent on health care provider characteristics, where decentralized responsibilities and social factors interact. To evaluate this argument, costs estimation analyses are replicated at district and national levels. Findings of this analysis are presented in Table 4, for facility+district levels – columns (1)–(4) – and facility+district+national levels—columns (5)–(8). The results are consistent with findings presented for a facility level in Table 3, supporting the hypothesis that total costs are mainly affected by the performance at a local facility level and FIC scale factors.

4. Conclusions

By using a representative sample of health care facilities and an econometric model, the paper provides new evidence on an insufficiently explored topic in the literature, addressing a multivariate approach to analyze determinants of immunization production and costs. Under a centralized-fixed, facility based immunization program, human resources are major determinant in producing higher outputs (measured as FIC or as total doses administered). The paper brings also insights about differences in factors' productivity in immunization activities: investments in more time devoted to vaccination tasks and higher professional involvement result to be more relevant than increasing facility capacities, in mainly all production specification models.

Results on immunization costs estimations may contribute to the discussion about the relevance of health system organization in explaining programs' performance. In this case, the Moldova's centralized healthcare system based mainly on population attending to fixed facilities seems to reduce the impact of input prices in the definition of the program cost as a whole, leaving higher relevance to demand characteristics and scale factors. Furthermore, the analysis suggests that costs arising on a district and national level

are not relevant in driving total expenditures, and mostly facility level costs determine overall observed variability. Factors operating on a local level – such as managerial efficiency in distribution and utilization of resources – seem to have influenced not only the production of doses administered and children covered, but also their costs.

It will be most interesting to compare our results with those obtained from decentralized systems, where decision making for labor remuneration and/or purchase of inputs is decentralized to sub-national entities and/or facilities.

Finally, the scale of children to-be immunized impacts the production of the program, and affects its costs positively, although decreasingly. This fact suggests that in a scenario of countries with high urbanization rates, costs of covering the immunization gap is relatively lower, providing incentives to scale up not only in scale but also in scope, by involving new antigens.

Conflict of interest

There is no conflict of interest with regard to this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine. 2014.12.041.

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