

Costs and cost-effectiveness of tuberculosis cultures using solid and liquid media in a developing country

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SUMMARY

SETTING: The expansion of culture has been proposed to aid tuberculosis (TB) control in developing countries.

OBJECTIVES: To examine the cost and cost-effectiveness at the Zambian National TB Reference Laboratory of homemade and commercially produced Löwenstein-Jensen culture (HLJ and CLJ) as well as automated and manually read liquid culture (AMGIT and MMGIT).

DESIGN: Costs were estimated from the provider's perspective and based on the average monthly throughput. Cost-effectiveness estimates were based on yield during the study period.

RESULTS: All techniques show comparable costs per culture (between US\$28 and \$32). Costs per *Mycobacterium tuberculosis* specimen detected were respectively US\$197, \$202, \$312 and \$340 for MMGIT, AMGIT,

CLJ and HLJ. When modelled for the maximum throughput, costs were above US\$95 per *M. tuberculosis* specimen detected for all techniques. When only performed among smear-negative specimens, costs per additionally identified *M. tuberculosis* would be US\$487 for MMGIT and higher for other methods.

CONCLUSION: Based on cost-effectiveness grounds, liquid media compare well with conventional solid media, especially where yield of MGIT is substantially higher than that of LJ media. The results indicate high overall costs per culture; the expansion of culture to decentralised levels with lower throughputs may result in even higher costs.

KEY WORDS: tuberculosis; cost-effectiveness; culture media; developing countries; Zambia

WHILE THE TREATMENT of tuberculosis (TB) is considered one of the most cost-effective interventions in health care,¹ we are still without a fast and simple diagnostic test that would be applicable in high-burden but resource-poor settings.^{2,3} This is particularly pertinent in regions where human immunodeficiency virus (HIV) prevalence is high, such as sub-Saharan Africa where, without better diagnostic tools, the TB-associated targets of the Millennium Development Goals are unlikely to be reached.⁴

While the diagnosis of TB in low-income countries has largely relied on direct sputum smear microscopy,^{4,5} culture of sputum on solid media still represents the gold standard for diagnosing *Mycobacterium tuberculosis*.⁶ The new Stop TB Strategy and other statements by the Stop TB Department at the World Health Organization (WHO), the Treatment Action Group and the Foundation for Innovative New Diagnostics (FIND) stipulate the phased expansion of culture as regular diagnostic measures.^{7–9} The

emergence of extensively drug-resistant tuberculosis (XDR-TB) has highlighted still further the need for culture.^{10–12}

New culturing techniques using liquid media such as the Mycobacteria Growth Indicator Tube (MGIT) represent hope for a quicker and reliable alternative to conventional Löwenstein-Jensen (LJ) media if they were affordable in resource-poor settings. Studies in resource-rich settings have demonstrated that the liquid media-based culture methods are more sensitive and faster than solid media, but that there is a higher risk of bacterial contamination of cultures.¹³

Here we report the first comparison of the economic cost and cost-effectiveness of MGIT and LJ culture techniques in a resource-poor country setting.

METHODS

We performed an economic costing from the provider's perspective of four methods: home-made LJ media

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(HLJ), commercially acquired LJ (CLJ) (Becton Dickinson Diagnostics, Woodmead, South Africa), manually read MGIT (MMGIT), and automated MGIT (AMGIT) using BACTEC 960 (Becton Dickinson). Costs to patients for seeking TB care are reported elsewhere.¹⁴ The study was performed at, and with the collaboration of, the Ministry of Health Chest Diseases Laboratory (CDL), Lusaka, i.e., the Zambian National TB Reference Laboratory. Costs were collected in the first half of 2006.

We collected costs using the ingredients approach¹⁵ for all procedural steps that are required for culturing mycobacteria, starting from the collection of specimens within Lusaka (or the arrival of samples at the laboratory when sent from outside Lusaka) until the safe disposal of the waste matter. All samples, regardless of their smear status, were cultured on all four media. Cultures were identified as *M. tuberculosis* by microscopy, subculture and subsequent niacin strip test, and the costs of this have been included. The costs of subcultures for drug susceptibility testing (DST) were not included.

Costs were established by reviewing expenditures in the first instance, and from quotations of distributors in Zambia. Workload and time spent on procedures were observed for different batch sizes. Capital costs (for equipment and buildings) were depreciated and annualised over the estimated lifetime at a discount rate of 3%, as applied in similar studies.¹⁶ The lifetime of equipment and the amount of consumables used over time were estimated with the help of senior laboratory staff.

While routine sputum cultures are one of the main tasks of the laboratory, the laboratory also performed other duties at the time of study, including direct smears, DST, quality assurance, etc. Costs that were shared between these tasks were apportioned by a 'step approach' whereby the number of procedural steps was identified for culturing and other laboratory tasks. The cost of each piece of equipment was then divided by the number of steps it was required for. To obtain cost per culture, cost per step was then multiplied by the number of steps in which the equipment was used during the culturing process.

We differentiated between 'culture-specific costs' and 'overhead costs', whereby culture-specific costs were related to one or more steps during the culturing process and overheads related to maintenance, cleaning, management, utilities and capital costs that were not a specific part of the culturing process. Overhead costs were apportioned corresponding to the workload of the various tasks.

For cost-effectiveness, we calculated the cost per processed culture and the cost per identified *M. tuberculosis* specimen. For the latter, we took the varying yields of *M. tuberculosis* isolation of the four methods into account. These were derived from the results of a MGIT demonstration study at the same labora-

tory, in which routine clinical samples were all cultured in parallel on the four culture systems so that yield could be accurately compared (Muyoyeta et al., submitted). We also calculated incremental costs for each additionally identified *M. tuberculosis* specimen where it was assumed that cultures would only be performed on specimens in which the direct smear was negative.

For costing purposes, we considered all contaminated results as 'negative', as they require processing of an additional specimen; thus, cost implications from the provider's perspective are identical to a negative result.

Some of the major assumptions were later varied in a sensitivity analysis: for the costs of the MGIT equipment and consumables, we applied the tariffs for low-income countries as negotiated between FIND and the supplier. In the sensitivity analysis, we varied this to the market price. In the base case scenario, we applied the average number of cultures processed between January 2005 and June 2006 (240 per month).¹⁷⁻¹⁹ In the sensitivity analysis, we later modelled this throughput to double (480 per month) and maximum throughputs (1280 per month) that are currently possible as dictated by the capacity of the two MGIT machines installed, taking into account the maximum time to result for all samples.

As the difference in yield of *M. tuberculosis* isolation between LJ and MGIT was found to be comparatively greater than in other studies, a sensitivity analysis was also performed around the difference in yield. For this, we modelled the yield of MGIT being 1.15 times the yield that we had identified for LJ based on a meta-analysis of MGIT and LJ comparative studies.¹³

The study did not involve human subjects and therefore did not require ethical approval.

RESULTS

The total costs per culture were calculated respectively at US\$29, \$28, \$31 and \$32 for HLJ, CLJ, MMGIT and AMGIT. In the case of HLJ under the current rate of throughput, roughly two thirds (US\$18, 61%) of the total cost per culture are made up of overhead costs. Running costs, such as rent of the building, utilities and vehicle running costs, form the bulk of the overhead costs, followed by staff costs for management and support staff. The culture-specific costs (US\$12, 40%) comprise equipment (US\$5, 16%), consumables (US\$6, 19%) and staff costs (US\$1, 5%). A breakdown of the costs for the other three culturing methods is shown in Table 1.

Costs per identified *M. tuberculosis* case vary substantially with the method used, due to the different *M. tuberculosis* yields. Positive cultures, irrespective of the culture method used, were subjected to a niacin strip test to identify *M. tuberculosis*. Early results of the MGIT demonstration study indicate a yield (of

Table 1 Costs in US\$ per culture and per identified *M. tuberculosis* case by various culture techniques (rounded to the nearest US\$)

	Homemade LJ		Commercial LJ		Manual MGIT		Automated MGIT	
	Per culture	Per positive <i>M. tuberculosis</i> specimen	Per culture	Per positive <i>M. tuberculosis</i> specimen	Per culture	Per positive <i>M. tuberculosis</i> specimen	Per culture	Per positive <i>M. tuberculosis</i> specimen
Culture-specific costs								
Consumables	6	64	5	52	7	45	7	45
Equipment	5	53	4	46	4	25	5	34
Staff	1	17	1	15	2	11	1	8
Subtotal	12	134	10	113	13	81	14	87
Overheads	18	206	18	199	19	116	18	115
Total	29	340	28	312	31	197	32	202

LJ = Löwenstein-Jensen; MGIT = Mycobacteria Growth Indicator Tube.

confirmed *M. tuberculosis*) of roughly 9% for both solid media techniques (HLJ and CLJ) and 16% for both liquid media techniques (MMGIT and AMGIT). Taking the varying yields of all four methods into account, we calculated the cost per identified *M. tuberculosis* specimen to be respectively US\$340, \$312, \$197 and \$202 for HLJ, CLJ, MMGIT and AMGIT. Incremental costs per identified *M. tuberculosis* specimen, assuming culture was only performed on the smear-negative samples, were greater, at US\$732, \$635, \$487 and \$500 for HLJ, CLJ, MMGIT and AMGIT, respectively.

When modelling increased throughput rates (from currently 240 to 480 and a maximum of 1280 specimens per month), total costs per identified *M. tuberculosis* specimen changed from US\$340 to \$232 and \$146 for HLJ, from US\$312 to \$187 and \$129 for CLJ, from US\$197 to \$141 and \$97 for MMGIT and from US\$202 to \$142 and \$98 for AMGIT when change of throughput was modelled from current to double and maximum levels, respectively. While culture-specific costs per identified *M. tuberculosis* changed from

US\$134 to \$110 and \$94 in the case of HLJ, the overhead costs changed far more, from US\$206 to \$121 and \$53. Changes in the other three methods are comparable (Figure). When changing the price of MGIT equipment and consumables from FIND negotiated prices to market prices, the cost per culture changed from US\$31 to \$34 for MMGIT and from US\$32 to \$37 for AMGIT. The cost per identified *M. tuberculosis* changed from US\$197 to \$217 for MMGIT and from US\$202 to \$232 for AMGIT.

When varying the yield of MGIT to be 1.15 times the yield of LJ methods, the cost per culture hardly changed, while the cost per identified *M. tuberculosis* specimen changed from US\$197 to \$321 for MMGIT and from US\$202 to \$329 for AMGIT. The cost for LJ remained identical per definition.

Changes to the exchange and discount rates were insignificant (data not shown).

The most costly line items that drive the cost per culture and per positive *M. tuberculosis* case are shown in Table 2. Some of these costs are proportional to the number of cultures processed, such as MGIT tubes,

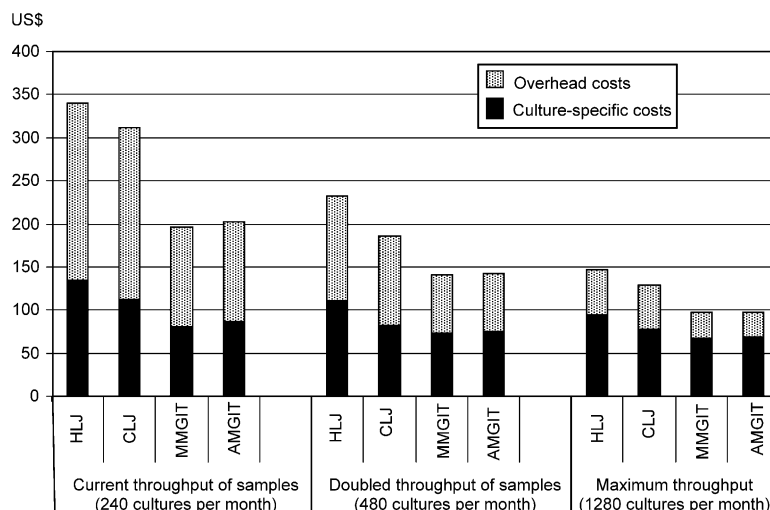


Figure Cost comparison per identified *M. tuberculosis* case considering varying degrees of throughput of samples. HLJ = home-made LJ media; CLJ = commercially acquired LJ media; MMGIT = manually read MGIT; AMGIT = automated MGIT; MGIT = Mycobacteria Growth Indicator Tube; LJ = Löwenstein-Jensen.

Table 2 Most important cost drivers (>US\$0.20 per culture), their unit costs and cost per culture (cost per culture includes multiple units if more than one unit is required to process one culture)

	Unit	Unit cost	Homemade LJ	Commercial LJ	Manual MGIT	Automated MGIT
Consumables						
MGIT tubes	Piece	2.43			2.43	2.43
Inoculation loops	Piece	0.80	0.96	0.97		
LJ slants	Piece	0.59	0.06	0.65		
Centrifuge tubes	Piece	0.56	0.66	0.66	0.66	0.66
MGIT decontamination reagent (PANTA)	15 ml	9.48			0.51	0.51
Pasteur pipettes	Piece	0.27	0.35	0.35	0.69	0.69
Phenol	500 g	24.66	0.26	0.26	0.31	0.31
Decontamination reagent (Mycoprep)	150 ml	7.05	0.23	0.23	0.23	0.23
Immersion oil	50 ml	72.17	0.22	0.22	0.24	0.24
Other			2.78	1.28	2.07	2.06
Equipment						
Centrifuge		6930.00	1.97	1.97	1.97	1.97
MGIT machine		5682.00			0.00	1.62
Incubator		1718.00	0.46	0.46	0.44	
Autoclave		3535.00	0.47	0.48	0.45	0.45
Biosafety cabinets		944.00	0.24	0.24	0.23	0.23
Distiller		2105.00	0.28	0.28	0.27	0.27
Computer		1592.00	0.24	0.24	0.24	0.24
Other			0.94	0.45	0.45	0.70
Staff (laboratory)						
Laboratory technologist	Per day	51.00	1.43	1.30	1.71	1.22
Other			0.01	0.01	0.02	0.02
Overheads						
Building	Per day	76.49	2.58	2.58	2.69	2.67
Electricity	Per day	41.73	1.41	1.41	1.47	1.46
Fuel	Per day	25.91	1.40	1.40	1.46	1.45
Maintenance	Per day	40.38	1.36	1.36	1.42	1.41
Vehicles (capital costs)	Per vehicle	28857.00	1.33	1.33	1.39	1.38
Water	Per day	34.77	1.17	1.17	1.22	1.21
Other						
Running costs			1.46	1.46	1.52	1.51
Consumables			0.47	0.47	0.55	0.55
Equipment and furniture			1.57	1.58	1.64	1.63
Administration/support/management staff			4.97	4.98	5.18	5.15
Total cost/culture			29.28	27.82	31.47	32.28

LJ = Löwenstein-Jensen; MGIT = Mycobacteria Growth Indicator Tube; PANTA = polymyxin B, amphotericin B, nalidixic acid, trimethoprim, azlocillin.

inoculation loops, LJ slants, etc. Other line items are shared costs, and are thus not proportional to the number of cultures. These costs are subject to economies of scale. Among overhead costs, building rent, utilities and maintenance represent the most prominent cost drivers.

DISCUSSION

The operational effectiveness of MGIT and its superiority over solid media (LJ) in terms of its sensitivity and speed has been demonstrated across high-income countries.^{20–28} What remains to be demonstrated is its effectiveness and cost-effectiveness in resource-poor settings, which bear the highest burden of TB. The results of this study show that, although the actual medium is cheaper for LJ methods, the overall cost per culture is comparable between the four methods in USD.^{28–32} Moreover, the greater sensitivity of the MGIT methods leads to substantially lower costs per identified *M. tuberculosis* specimen of both MGIT methods (manual MGIT in particular) compared to

the LJ methods (Table 1). Despite the large capital outlay needed to buy an automated MGIT instrument, there was relatively little difference in overall costs between the two MGIT methods. Costs per identified *M. tuberculosis* specimen—and even more so the incremental cost per additionally identified smear-negative, culture-positive *M. tuberculosis* specimen—are largely dependent on the proportion of positive samples. In settings with higher or lower yields, therefore, the cost-effectiveness ratios will change. In this study, MGIT (especially manual MGIT) performed substantially better than LJ in detecting positive samples overall, and smear-negative, culture-positive TB in particular. This explains the wide differential in the incremental costs between these methods. When modelling yield differences between MGIT and LJ that were found in previous studies,¹³ the cost per identified *M. tuberculosis* specimen was comparable between solid and liquid media: MMGIT showed a cost of US\$320 compared to a cost of US\$312 for CLJ.

The considerable differences in total cost and overhead cost when considering various throughputs (i.e.,

number of cultures processed over time) demonstrate the effect of the efficiency of the laboratory on the costs per sample and on cost-effectiveness. When comparing the current level of throughput (240 cultures per month) to the potential maximum throughput (1280 per month), given the number of MGIT machines currently installed, the total cost per identified *M. tuberculosis* specimen dropped to less than half, while the overhead cost per identified *M. tuberculosis* dropped to almost a quarter (Figure).

However, even when the maximum throughput of cultures is considered, costs per identified *M. tuberculosis* case are still high, with the total cost per *M. tuberculosis* positive culture ranging from US\$97 to \$147. While it would be possible to increase the throughput by purchasing more equipment, it is unlikely that further economies of scale could be achieved to a great extent, as some of the major cost drivers consist of line items that are proportional to the number of cultures (Table 2).

Our estimates are based on preferred pricing of equipment and consumables negotiated between FIND and the manufacturer for low-income countries. In the future, bulk purchasing on a global scale as applied by the Global Drug Facility (GDF) for TB drugs, which uses pooled demand, systematised forecasting and competitive bidding processes, may further lower the costs of equipment and consumables for diagnostics, including culture.^{29,30}

Our analysis has some limitations, in that the cost-effectiveness results do not take into account the multiple benefits of the shorter duration of the MGIT vs. the LJ culture. These include earlier initiation of treatment, with consequently faster recovery and potentially lower case fatality. Moreover, the shorter time-to-result may increase clinicians' recognition of culture results before starting (presumptive) treatment. All this would lead to additional savings that were not part of this analysis. Furthermore, the perspective of our study is that of a provider and thus does not take other costs into consideration such as those incurred by the patients and their families. We have only included transport costs for cultures from within Lusaka, and not for samples requiring transport for longer distances.

However, our results do inform the debate on extending the use of culture in resource-poor settings, as is currently advocated.^{6-9,31} There are two major reasons for expansion of TB culture; first, to diagnose more smear-negative TB, particularly in HIV-positive individuals, and second, to provide information on drug resistance. For the first of these reasons, the revised recommendations from the WHO include the culture of sputum from all HIV-positive individuals who are found to be sputum smear-negative. We therefore also modelled the costs of culturing smear-negative cultures only (i.e., the incremental cost of identifying one additional *M. tuberculosis*-positive specimen if the smear showed a negative result). With the cheapest

method (MMGIT), costs per additionally identified TB case were US\$321 per *M. tuberculosis*-positive culture. While this cost seems high, it requires consideration in the light of the potential benefit both for the patient and the health system. If adding culture will result in more patients with TB getting a rapid and accurate diagnosis and reduced transmission, then the cost may be justified. However, research by Munyati et al. indicated little added clinical benefit of culture over smear microscopy, as only very few cases had received a smear-negative but culture-positive diagnosis.³² Moreover, in only a few cases had the culture result preceded TB treatment.³² Improving the quality and quantity of sputum submitted for examination³³ and the sensitivity of sputum smear, for example by using fluorescent microscopy, will be cheaper than sputum culture;³⁴ this and other available improvements to sputum smear diagnosis should therefore be carefully considered.

As for diagnosing cases of resistant TB, it is likely that most countries will limit the cultures performed to those either with recurrent TB disease or those failing a first-line regimen. Due to the impact of efficiency, laboratories where lower levels of throughput are expected (e.g., in smaller peripheral laboratories) may be subject to significant diseconomies of scale, with high equipment and overhead costs per culture. With limited numbers of cultures, it may thus be more efficient to maintain centralised culture facilities, with all their limitations, rather than to try and decentralise.

Newer diagnostics are urgently needed that are sensitive and specific (especially in HIV-infected individuals), rapid and affordable. Affordability is a relative concept, but any new diagnostic test needs to provide maximum benefit from the scarce resources available.³⁵

CONCLUSION

Our research shows that costs per culture in a resource-poor setting are comparable between all four techniques, but that both MGIT methods appear superior to conventional LJ in terms of cost-effectiveness due to the higher yield of the MGIT. Even when a lower difference in yield between MGIT and LJ is taken into account, MGIT is still comparable to LJ in terms of cost while offering a faster time to result.

The impact of the level of throughput on efficiency suggests that this needs to be taken into consideration and compared to potential travel costs before embarking on policies to decentralise *M. tuberculosis* culture processes.

The results also indicate that culture, irrespective of the technique, comes at a high cost per case diagnosed, which may limit the expansion of culture without significant additional resources.

Ultimately, the development of simple, fast and less costly diagnostic tools is urgently needed.²⁴

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R É S U M É

CONTEXTE : L'expansion de la culture a été proposée pour faciliter la lutte antituberculeuse dans les pays en développement.

OBJECTIFS : Etudier le coût et le rapport coût-efficacité au Laboratoire National de Référence de la Tuberculose en Zambie, à la fois pour les cultures sur milieu de Löwenstein-Jensen produit sur place (HLJ) ou commercialement (CLJ) ainsi que pour les cultures sur milieux liquides lues de manière automatique (AMGIT) ou manuelle (MMGIT).

SCHEMA : On a estimé les coûts dans la perspective du pourvoyeur et on s'est basé sur le débit mensuel moyen. Les estimations de coût-efficacité ont été basées sur le rendement au cours de la période d'étude.

RÉSULTATS : Les coûts par culture sont comparables avec toutes les techniques (entre 28 et 32 US\$). Les coûts par échantillon de *Mycobacterium tuberculosis* détecté ont été de 197 US\$ pour MMGIT, de 202 pour AMGIT,

de 312 pour CLJ et de 340 pour HLJ. Après modélisation pour le débit maximum, les coûts sont supérieurs à 95 US\$ pour tout échantillon de *M. tuberculosis* détecté, quelle que soit la technique. Si les cultures sont pratiquées exclusivement sur les échantillons négatifs à la bacilloscopie, les coûts par *M. tuberculosis* identifié en supplément seraient de 487 US\$ pour MMGIT et plus élevés encore pour les autres méthodes.

CONCLUSION : Si l'on se base sur le rapport coût-efficacité, les milieux liquides se comparent favorablement aux milieux solides conventionnels, particulièrement là où le rendement de MGIT est substantiellement plus élevé que celui des milieux de LJ. Ces résultats indiquent des coûts globalement élevés par culture ; l'expansion de la culture vers des niveaux décentralisés à débit plus faible peut entraîner une augmentation supplémentaire de ces coûts.

R E S U M E N

MARCO DE REFERENCIA : Se ha propuesto la ampliación de los cultivos de *Mycobacterium tuberculosis* con el fin de optimizar el control de la enfermedad en los países en vías de desarrollo.

OBJETIVOS : Examinar en el Laboratorio Nacional de Referencia de Tuberculosis de Zambia el costo y la rentabilidad del medio de cultivo Löwenstein-Jensen (LJ) obtenido comercialmente (CLJ) y el producido en forma local (HLJ) y del sistema de tubos indicadores de crecimiento bacteriano en medio líquido con lectura automática (AMGIT) o manual (MMGIT).

MÉTODO : Los costos se calcularon a partir de los prospectos de los proveedores y con base en la cadencia mensual promedio. El cálculo de la rentabilidad se hizo con base en el rendimiento durante el período de estudio.

RESULTADOS : Se observó que todas las técnicas ofrecen un costo equivalente por cultivo (entre 28 dólares y 32 dólares). Los costos por detección de una muestra

positiva de *M. tuberculosis* fueron de 197 dólares con el MMGIT, 202 dólares en AMGIT, 312 con medio CLJ y 340 con medio HLJ. Cuando se simuló una máxima cadencia, los costos sobrepasaron 95 dólares por cada muestra positiva detectada con todas las técnicas. Si se practica únicamente el cultivo de las muestras con baciloscopia negativa, el costo de detección de *M. tuberculosis* en una muestra adicional sería de 487 dólares con el MMGIT y sería superior con los demás métodos.

CONCLUSIÓN : Desde la perspectiva de la rentabilidad, los medios líquidos son equivalentes a los medios sólidos convencionales, en particular cuando el rendimiento del MGIT es netamente más alto que el de cultivo en medio LJ. Estos resultados señalan altos costos globales por cultivo ; la expansión de los cultivos a niveles descentralizados del sistema de salud que tienen cadencias menores, podría derivar en costos aun más altos.