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A critique of the paper "The estimated costs of production and potential prices for the World Health Organization Essential Medicines List"

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ABSTRACT

Identifying and addressing challenges to improving access to drugs on the WHO Essential Medicines List (EML) has been the subject of significant research, see, for example, the Lancet Commission (Wirtz et al, 2017.) In this paper we review "Estimated costs of production and potential prices of medicines for the World Health Organization Essential Medicines List" (Hill et al., 2018) in which the authors argue for "greater transparency in drug pricing" and propose generating estimates of the cost of manufacturing essential medicines to inform negotiations on drug pricing.

We are not convinced that use of a costing exercise to negotiate generic drug prices is merited irrespective of the quality of the analysis. The implication that prices should be reduced to the level predicted by a model is likely to lead to an increase in generic drug shortages. The way to tackle generic drug prices is through more effective procurement arrangements (Danzon, Mulcahy and Towse, 2015) which brings in competitive global suppliers. More efficient medicines prices may only be achieved by bringing in regional or global suppliers who are more efficient than local producers. Price transparency could help payers understand how effective their generic procurement process appeared to be. However, price transparency also conveys information to suppliers.

Although Hill et al. (2018) set out that 85% of EML drugs are generic, the authors discusses the use of cost estimates and the removal of patent protection in the context of on-patent drugs. However, in many markets some recovery of R&D cost is both to be expected and is necessary. Health Technology Assessment (HTA) is the tool that can inform price negotiation or decisions about use of a product. In some low income markets or for some low income population groups we might expect to see tiered pricing bringing prices close to generic levels. Governments and international organisations could usefully seek to facilitate the use of tiered pricing.

The authors examined data on exports from India of active pharmaceutical ingredients (API). The authors assume a static conversion cost of $0.01 USD mainly base on previous estimation for India, this ignores that marketing and distribution costs can vary considerably between countries and markets. The results are sensitive to the conversion cost selected, and although the authors have demonstrated this in other publications it is not highlighted in this article. They compare this information with minimum current drug prices in India, South Africa, and the UK. The methodology used in the article is problematic for a number of reasons and we find that the conclusions are not supported by the results. The model is not a good predictor of price. In India, 47% of medicines have observed prices that are 50% lower than the projected efficient price. In contrast, the authors' analysis shows that 78% of the prices observed in South Africa are in the range of three times above or below the estimated prices and around 60% of the medicines included for the UK have prices three times above the estimated price.

We are not convinced about either the value of a costing exercise or of the accuracy of the one undertaken by the authors.

1. INTRODUCTION

Improving access to essential medicines is one of the key objectives of the World Health Organization's (WHO) pursuit of universal health coverage. Identifying and addressing challenges to improving access to drugs on the WHO Essential Medicines List (EML) has been the subject of significant research, see, for example, the Lancet Commission (Wirtz et al, 2017.) One important part of this is pricing. In this paper we review "Estimated costs of production and potential prices of medicines for the World Health Organization Essential Medicines List" (Hill et al., 2018) ("the article"), in which the authors argue for "greater transparency in drug pricing" and propose generating estimates of the cost of manufacturing essential medicines to inform negotiations on drug pricing. In this paper we set out their approach and critique it, looking at both the policy implications of using cost estimates as a basis for pricing policy and the issues raised by their estimation methods and results.

2. SUMMARY POINTS OF THE ARTICLE

The authors make two summary points in their conclusion to which we respond:

1) They conclude that "many medicines that are sold at prices far higher than would be expected based on their production costs" (Hill et al. (2018), p. 6).
2) They suggest that "Generic price estimation and international price comparisons can be expanded to empower government price negotiations, and to support cost-effectiveness calculations at international and national levels"(Hill et al. (2018), p. 6).

Whilst we agree that it is almost certainly the case that some prices are far above costs, it is also very likely that, in other cases, production is inefficient and costs are too high. Lower prices come from effective procurement arrangements and the use of competition. Evidence from Danzon et al. (2015) indicates that international agencies get better prices because they use competition. This is likely to be a more effective route to lower prices than estimating costs. Whilst the two approaches are not mutually exclusive, it is hard to see what the cost estimates add, particularly if the method of validating the cost estimates involves looking at prices elsewhere. It would be quicker to compare prices obtained through competition with observed prices elsewhere.

More generally, we are unconvinced that the exercise of estimating the cost of manufacturing medicines adds very much to an analysis of prices in the most competitive international markets. This is for two reasons:

a) The model is not a good predictor of price. In fact, the methodology proposed in the article is problematic, as demonstrated by the results which also show that many medicines are, according to this methodology, significantly *underpriced* in India. It is not clear, therefore, how the model can be validated; and
b) a direct price comparison and an examination of market dynamics and procurement arrangements is more likely to generate effective policy recommendations to achieve lower sustainable generic prices.

We set out more fully our analysis on a) and b) in subsequent sections of the paper.

The article does not clearly distinguish as to whether particular points relate to generic medicines or on-patent medicines. Indeed the Discussion section puts much focus on issues concerning patents, compulsory licensing and TRIPs flexibilities when the article states that 85% of the 2017 EML medicines were generic. Beall and Attaran (2016) state that only single digit percentages of medicines on the 2013 and 2015 EML were under patent. In any event, the article spends some time discussing patent issues when the vast bulk of medicines on the EML are generic and patent coverage is low in many developing countries. On-patent drug prices reflect not only current production cost but mark-ups to provide a return on past investment in research and development. Estimates range from $1.5bn to $2.4 billion to research one approved new pharmaceutical compound (Mestre-Ferrandiz et al., 2012; DiMasi et al., 2016). As the authors recognize, one of the limitations of their analysis is "the inability to include an estimate for the costs of product development, bioequivalence studies, registration costs and costs of litigation". The extensive discussion of patent issues in a paper analysing the prices of generic medicines seems odd as the sorts of policy approaches discussed would have no impact on the price of medicines already genericized.

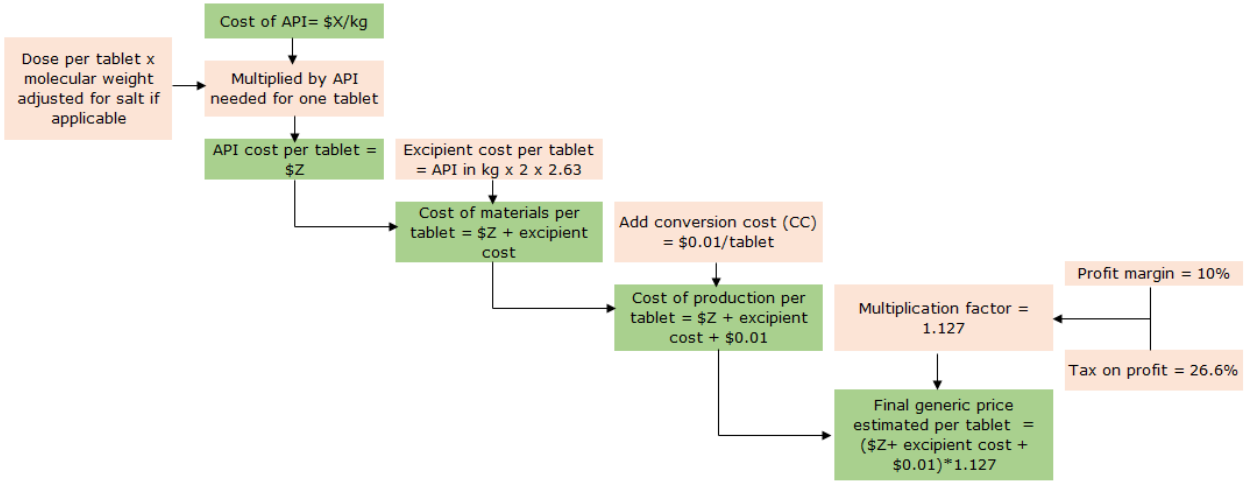
It is perhaps helpful to set out the policy implications of their analysis:

- In the case of on-patent products, the underlying issue is how lower prices can best be achieved in a way that increases access whilst preserving adequate returns to R&D to ensure continuing innovation. Referencing the prices of newer, innovative medicines to the cost of manufacturing of runs the risk of compromising patient access to new medicines in the future. Use of Health Technology Assessment (HTA) in order to determine whether scarce resources should be used on a new treatment at a particular price is a more efficient way of determining an acceptable price;
- In the case of generic drugs, competition is key, as the authors recognise has been so beneficial in the cases of HIV, TB and malaria. Does a costing exercise help this process? Hill et al. (2018) state that it can inform negotiations. However, an effective competitive process does not involve price negotiations – it *replaces* price negotiation. At best, cost estimates could help payers understand how effective their generic procurement process appeared to be;
- Would it make sense to set generic prices using their cost estimates? Although the authors do not make this policy recommendation, it is, we would argue, one possible conclusion. However, context is always different and price setting for generic drugs risks either (i) setting price too low, leading to shortages or (ii) signalling to suppliers a willingness to pay which reduces price competition.
- Does price transparency help? In the case of on-patent products, it risks linking markets, reducing access in low income countries. In the case of generic medicines, as in the case of cost estimates, it could help payers understand how effective their generic procurement process appeared to be. However, price transparency also conveys information to suppliers.

3. METHODOLOGY

The article examined export data from India of active pharmaceutical ingredients (API). The authors used the export price and weight to estimate an average API price per-kilogram for drugs on the WHO Model List of Essential Medicines (EML). They added in an assumed excipient cost, a manufacturing conversion (into tablets) cost, and a profit margin of 10% after tax (as illustrated in Figure 1). They estimate the price of approximately 35% of the drugs listed in the EML (according to WHO (2017a), 433 medicines are listed in the EML). Finally, they compare this information with minimum current drug list prices in India, South Africa, and the United Kingdom.

Figure 1. Algorithm used by Hill et al (2018) to estimate generic prices.



Source: Adapted from Figure 1 in Hill et al. (2018), "Estimated costs of production and potential prices of medicines for the World Health Organization Essential Medicines List"

There are a number of assumptions in the calculations that are problematic. First, the authors based the price estimation on data on active pharmaceutical ingredients (API) exported from India. Costs of production in India are among the lowest in the world and it would not be realistic to assume that other countries could produce at the same price as India. Low production costs and prices have allowed India to become one of the fastest-growing pharmaceutical markets globally and established India as a global manufacturing base. All this is reflected in the importance of Indian pharmaceutical products to many middle and low income countries (MLICs). India has multiple factors, including the large raw material base and the availability of a skilled workforce, which give the country a competitive advantage. This specific situation would be difficult to replicate in other markets. It could be argued that this is a useful indicator of minimum costs of production, but it is clearly not an estimation of costs that can be achieved in other contexts or countries. In any event, the results for India itself in the analysis raise questions about the validity of the model and the overall approach being proposed, because the analysis suggests that more than 60% of medicines in India were below a supposedly sustainable generic price (Hill et al. (2018), p. 4). The authors argue that this indicates that their price estimates are "conservative". It could be argued that they are simply inaccurate. It illustrates the risks of using this approach as a replacement for

well-designed procurement policies that promote long-term competitive and sustainable medicines markets.

Conversion costs (operating expenditures minus API and excipients) are needed to convert raw API into a final pharmaceutical product. The authors assumed a static conversion cost of $0.01 USD based on discussion with large Indian generic manufacturers and the results of the study done by Chaudhuri and West (2015) getting confirmation from one Indian Government price control order[1]. Marketing and distribution costs can vary considerably between countries and markets. For instance, Pinheiro et al. (2006) presents values over $0.05 which are five times the value used by the authors. Hill et al. (2018) note that the lowest prices in South Africa and the UK are close to those estimated by Chaudhuri and West (2015). The authors find that their results prove to be highly sensitive to changes in estimates of the conversion cost. An earlier paper by the authors included sensitivity analyses for the case of India that showed a substantial effect of the level of conversion costs on the results[2]. A robust literature review is required to explore the level of conversion costs and provide a clear picture of the variability between countries. Sensitivity analysis that explores variations in the conversion cost should also be undertaken in the comparisons with South Africa and the UK.

Costs excluded from the analysis are those related to the manufacturing output that cannot be sold. For example, samples to be drawn or batches rejected for quality control reasons. In addition, the costs associated with establishing and maintaining market authorization across multiple markets, which could be significant, are not included. The cost of obtaining market authorization for generics is lower than for branded innovative medicines, as are the initial pharmacovigilance requirements. However, pharmacovigilance is needed for generic products and is a cost to the manufacturer.

4. RESULTS

We consider that the conclusions are not supported by the results. The authors conclude that "Estimation of generic prices can identify many medicines that are sold at prices far higher than would be expected based on their production costs" (Hill et al. (2018), p. 6). Equally, however, the data presented in the accompanying appendix, and not discussed in the article, also shows a significant number of medicines that sell *below* the price expected based on their production costs as we set out in Table 1 below. This suggests potential flaws in the approach being proposed. The data presented in the appendix do *not* show that most drugs can be produced at lower prices than those at which they are currently sold. The authors note that circumstances particular to the Indian medicines market, such as the interaction of the public schemes with private market, may be contributing to the apparent wide range of medicines being sold below viable levels. This underlines our concern about the value of the methods proposed in the article to estimate costs of production and then use the information to support price negotiations.

[1] There is also a reference to a McKinsey 2014 report "Outlook on Pharma Operations."
[2] We were able to review a paper dated January 2017 by the authors entitled "Analysis of the costs of production of medicines in the World Health Organization Model List of Essential Medicines."

Table 1. Comparison between estimated prices and the current prices*

	UK		SA		India	
Price Ratio**	**Medicines**	**%**	**Medicines**	**%**	**Medicines**	**%**
<= 0.5	16	6.2	18	9.0	135	47.0
[0.5 , 1]	41	15.8	49	24.6	50	17.4
[1, 1.5]	27	10.4	42	21.1	28	9.8
[1.5 , 2]	22	8.5	18	9.0	20	7.0
[2, 3]	30	11.6	29	14.6	23	8.0
[3 , 5]	21	8.1	14	7.0	18	6.3
[5 , 10]	24	9.3	16	8.0	7	2.4
[10 , 20]	21	8.1	5	2.5	5	1.7
[20, 50]	19	7.3	4	2.0	1	0.3
[50 , 100]	20	7.7	2	1.0	0	0.0
>100	18	6.9	2	1.0	0	0.0
Total***	**259**	**100**	**199**	**100**	**287**	**100**

*Current price/estimated price **Ratio of observed price to estimated price *** We have analysed the data supplied by the authors in the Supplementary appendix. The totals differ from those they use in the text of the paper (UK:277; SA:212; India: 298). This means that our %ages differ slightly from those used by the authors in their paper.
Source: Information extracted from the reported estimations, Hill et al. (2018) – Supplementary appendix.

In the comparison of estimated generic prices to current prices in India (Table 1), the results indicate that nearly two thirds (64%) of Indian prices were lower than the estimated generic price. The data shows that nearly half (47%) are priced more than 50% below the estimated price.

The comparison of estimated generic prices to current prices in South Africa shows two extreme data points (ondansetron and mercaptopurine, both branded drugs[3]) and over 60% of prices above the estimated generic price[4]. However, around 30% of those prices are less than one time above the current price and 34% are below the estimated price.

The comparison of estimated generic prices to current prices in the UK suggests that 39% of the medicines included have prices five times or more above the estimated price and 38% of estimated prices are between one and five times the observed prices. However, the list prices publicly available in the UK are in general higher than the actual prices paid. This because of multiple mechanisms including, for generic products, hospital tendering and competitive discounting to community pharmacists, and for on-patent products, confidential discounts. The paper states that confidential discounts "are typically in the order of 30% of the prices stated in this report." This estimate is not referenced.

[3] Ondansetron (24mg) price for SA listed in gastrointestinal medicines is 137 times higher than the estimated price. Mercaptopurine listed in antineoplastics and immunosuppressives is 106 times higher.

[4] We analysed the data listed in the appendix and found small differences in what is reported in the article and what is in the database. The article says 67% and 212 drugs. We found 199 and 63%. Similarly with India we found less prices listed in the appendix in comparison to the text.

The analysis assumes that APIs are purchased from a third party and uses API prices from the Indian export market. The manufacture of APIs is the most expensive aspect of generic pharmaceutical production because of the investment in equipment, quality assurance and skilled labor force. APIs prices for WHO EML medicines based on India exports cannot be directly used by other countries to estimate their cost for essential medicines unless they are willing to import API or finished generics from India. There is a case for encouraging global competition for generic contracts and it may well be that this leads to more APIs or finished generics being imported from India. Encouraging such competition is likely to be more effective in reducing prices than expecting local producers to price at a cost derived from data using Indian API export prices.

5. DISCUSSION

The discussion makes a number of statements that should be challenged. In our view, the authors are overstating the benefits of cost modelling and of pricing transparency.

1. "Assuming an absence of barriers to market entry, a wide range of the drugs on the EML can be profitably sold at very low prices in all countries." Whilst this may well be true, the model does not provide the evidence to support the claim. Cost structures may differ. It is likely that many local generic manufacturers have high costs relative to efficient global suppliers and that they also spend significant sums branding generics and promoting them to pharmacists and possibly to clinicians. The way to get lower prices is through more effective and transparent procurement arrangements (Danzon et al., 2015) and effective quality regulation such that branding of generics is not needed to signal quality. This will be more effective than modelling costs or seeking pricing transparency. The authors need to recognize that low prices may only be achieved by bringing in regional or global suppliers who are more efficient than local producers. Imposing a price on a local producer based on an estimate of cost, may well put them out of business, and in the absence of other low cost suppliers, lead to shortages. The assumption of the absence of barriers to market entry is an unrealistic assumption in the generics markets, given that there are a range of barriers including government preferential purchasing, import duties and taxes and tariffs on medicines, and uncompetitive in-country distribution and supply chains. Emphasis needs to be given to reducing these barriers, not estimating costs and observing prices from elsewhere.

2. The point that "lower costs for generics could drive down the prices of patented drugs in the same therapeutic area" may be true, but again depends on effective use of procurement and of Health Technology Assessment (HTA) to assess incremental benefits and incremental costs of different treatments, not on transparency or modelling costs based on API prices in India. It also risks inadvertently disincentivising the development of new medicines in that therapeutic area if the prices of patented drugs are manufacturing cost-plus rather than linked to the incremental health gain delivered.

3. The proposal that pricing policy could be based on cost of manufacture might not only be problematic from a methodological standpoint, but also risks setting benchmarks that may hinder the operation of competitive markets with multiple

generic suppliers. Pricing benchmarks set by governments convey signals and sometimes have a habit of becoming the market standard, even when a competitive market could drive lower, not higher, prices.

6. MARKET COMPETITION AND LONG TERM SUPPLY

The paper looks at the production cost of WHO EML drugs as a way of approximating the appropriate price level for price negotiation or price setting purposes. However, if prices end up fixed at an inefficient level, the wrong incentives will be sent to market participants. Objectives of improving access to medicines and generating new drugs may not be achieved.

The minimum price that will keep a company in the market is that which allows them to cover fixed and variable costs. This is the intention of the authors when they estimate minimum price through production costs. However, an accurate estimation of the most efficient production cost is difficult to achieve, as they demonstrate.

The theory of demand and supply equilibrium rests on the ability of a competitive market to achieve low prices by excluding the less efficient producers. In this regard, a generic market should promote efficiency by allowing the market to achieve an equilibrium price in which the demand is satisfied and only those manufacturers that are making full and efficient use of available resources can compete successfully at those prices. This is most likely to be achieved in a generic market with a high degree of competitiveness and with symmetry of information. Arguably, price disclosure to buyers, rather than cost estimation, is important in this context. Competitiveness has been an important part of the development of the pharmaceutical industry in India and is responsible for the current low prices observed in the market (United Nations, 2015). Indian industry is highly competitive, indeed highly competitive Indian pharmaceutical firms have been investing in R&D (Das and Das, 2015).

The low elasticity of demand associated with medicines hinders competitive market performance. It is the responsibility of policy makers to establish third party payers who can introduce procurement policies that increase demand elasticity and at the same time promote competition. Kaplan et al. (2012) argue that to have: a functioning medicines regulation authority; a robust market for generics; and aligned incentives for prescribers, patients and manufacturers, are necessary prerequisites for increasing the uptake and use of generic medicines. When the prices are jointly negotiated or negotiated by one institution, the power to bargain down prices increases, in part due to the volumes of sales on offer, and because asymmetry of information decreases. Hill et al. 2018 cite the example of generic entry that has decreased prices for HIV treatments in MLICs.

Cameron et al. (2009) analyse average public procurement prices for generics in a group of MLICs and conclude that they vary considerably. This suggests that whilst some countries procure medicines at competitive prices, procurement efficiency can be improved in many other countries. Transparency of process is needed to give confidence to global generic companies that competition will be fair, and also to reduce corruption in public procurement which decreases the benefit that competition brings to the accessibility and affordability of pharmaceutical products (United Nations, 2015).

There has been an increased interest in pricing transparency. However, pricing transparency is a means to an end (greater patient access to medicines) rather than an end in itself. It can hinder the use of tiered pricing in many circumstances by linking

markets together when buyers in one market reference the prices paid in another. In the case of off-patent medicines, buyer knowledge of what others have paid can increase understanding of how well their own markets for generics are working. However, general disclosure of transaction levels of generic prices may provide information to companies which reduces price competition.

Apart from the financial cost, there exist other economic costs that should be considered when looking at pricing transparency for on-patent products. For instance, pharmaceutical companies could delay access to new compounds in an attempt to avoid international reference prices or parallel trade which could negatively affect the price level (Kyle, 2007). The literature suggests that this has happened in the case of India where new drugs are entering the market later than other countries such as US and Germany (Berndt and Cockburn (2014). Transparency of on-patent prices links markets in a way that may hinder the recovery of R&D costs and reduce access to treatment.

Administrative pricing regulations and not competition policies appear to be leading efforts to improve access to affordable drugs (United Nations, 2015). However, fixed price regulation has the effect of reducing incentives to enter the market. Using IMS data for a group of high income countries (United Kingdom, Germany, France, Italy and Spain), Colak (2014) found more regulated environments are consistent with fewer generics and later generic entry.

There is also a gap between a government's capacity to secure low prices and increase access to pharmaceutical products. For instance, Kotwani et al. (2007) show that, although the procurement prices of medicines in the Indian public sector was under 0.5 times the international reference price, the median availability in the public sector ranged from 0 to 30 per cent. The lack of availability of certain drugs in India was also recognized in the Hill et al. (2018) article. This suggests that the problem is not price but lack of resources invested in public sector health care.

Patents do not necessarily mean that high prices will hinder patient access to new products in MLICs as manufacturers can price discriminate or tier price across countries according to, for example, levels of per capita income. Beall and Attaran (2016) note that for many of these countries, patents are not enforced or legislated, and that pharmaceutical companies do have pricing and access strategies in place to assist patient access to many patented medicines on the WHO Essential Medicines List. Although, tiered pricing is difficult to put in practice, it exists and improves the probability of accessing new compounds for patients in developing countries (Danzon et al., 2015). WHO could usefully seek to facilitate the use of tiered pricing. We note also that policy makers in different countries are using flexibilities in the Trade-Related Intellectual Property Rights agreement (TRIPS) to allow competition for some patented drugs, although the focus in Hill et al. (2018) on the use of TRIPs flexibilities appears odd, given that this does not impact on the pricing of the generic medicines which dominate the WHO EML.

When competitiveness is considered, the discussion of the production cost in a particular country or for a particular producer is of little relevance. Governments and international organizations should be looking at finding policies to develop competitive generic markets that improve pharmaceutical price determination and product quality.

7. CONCLUSIONS

We are not convinced that the costing exercise is validated by the analysis or the results. Operationalizing the costing exercise as proposed in the article will likely lead to an increase in generic drug shortages, a problem the global health community is already grappling with. This is because pushing prices below the costs of production for local manufacturers will lead to them making losses.

Improving efficiency and broadening the numbers of potential suppliers requires effective procurement and competition arrangements are in place that encourages local producers to improve efficiency and regional and global suppliers to enter the market. Hill et al. (2018) acknowledges the importance of this when discussing the successes of pricing arrangements for HIV and TB. Including a policy proposal on patents and TRIPs flexibilities in an analysis of costs does seem incongruous generic medicines dominate the WHO Essential Medicines List. However, cost-plus is not an appropriate approach to assess on-patent medicines. HTA should be used to assess the benefits and costs of using the treatment in a particular health setting. In some low-income markets or for some low income population groups we might expect to see tiered pricing bringing prices close to generic levels. WHO could usefully seek to facilitate the use of tiered pricing, whilst recognizing that in many markets some recovery of R&D cost is both necessary and to be expected.

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