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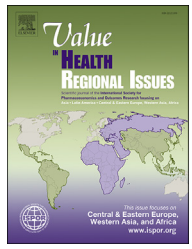

Economic Evaluation

Safety-Engineered Syringes: An Intervention to Decrease Hepatitis C Burden in Developing Countries—A Cost-Effectiveness Analysis From Egypt

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ABSTRACT

Introduction: To assess the cost-effectiveness of introducing the safety-engineered syringe (SES) to decrease hepatitis C burden resultant from unsafe injection practices in healthcare settings. **Methods:** A Markov process model for a hypothetical study cohort was developed over a 30-year time horizon to compare the adoption of SES use with the current strategy, conventional syringes (CS), in the Egyptian healthcare settings. The national treatment program was applied in both groups. Health benefits and total direct medical costs were estimated in both strategies. **Results:** The SES use demonstrated a reduction in the burden of injection-associated HCV infection because of unsafe practices in the Egyptian healthcare settings. The probability of HCV infection was 1.4% in the SES group and 40% in the CS group. Adoption of the SES use averted 177 hepatitis C cases and 157 hepatitis C–related deaths per 10 000 individuals. Introducing SES as a preventive strategy resulted in better quality-adjusted life-years (QALYs) (difference; 0.95 QALYs) and lower costs (difference; $–1712). **Conclusions:** Adoption of SES in the Egyptian healthcare settings is a more effective and cost-saving strategy. Our results are consistent with the WHO Injection Safety Program and Safe Injection Global Network initiatives, which call for adoption of smart syringes. The introduction of SES as one of the most urgently needed interventions is mostly encouraged to decrease hepatitis C burden in similar resource-limited settings. The use of SES as a prevention strategy may bring substantial population-level health gains and governmental cost savings in developing countries.

Keywords: burden, cost-effectiveness analysis, Egypt, hepatitis C, safety-engineered syringes, sharing

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Introduction

Hepatitis C virus (HCV) in Egypt, a lower-middle-income country (LMIC),[1] imposes a vast public health and economic burden. It disproportionately affects the poorest, with antibody and viremic prevalence twice as high as the wealthiest quintiles (12.7% and 9.5% vs 6.5% and 3.9%, respectively).[2] Each year, HCV transmission leads to 90 000 to 180 000 new infections[3,4] and over 30 000 liver-related mortalities in Egypt.[5]

The Egyptian government developed a national strategy for viral hepatitis (2008-2012) followed by an action plan (2014-2018) to decrease this burden.[6] The emphasis of the Ministry of Health and Population (MOHP) was providing treatment, with less attention given to prevention.[6] The National Committee for Control of Viral Hepatitis oversees a network of 164 treatment centers distributed across the country connected via an electronic database with an online registration system.[7] The cost of treatment coverage of 100% of viremics with fully subsidized oral direct antiviral agents (DAAs) ($534 million)—without taking into account the screening costs (174 million)—would represent 125% of the MOHP total 2016 and 2017 budget.[8]

The MOHP recently announced that 1.1 million cases have been treated at a total cost of 3.2 billion EGP since the introduction of DAAs in 2014.[7] Nevertheless, the annual treatment initiation rate is still low (around 5%), considering the ambitious goal of reducing viremic prevalence to <2% by 2025.[9] Simultaneously

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massive logistical efforts and resources will be required to scale up related screening services. So far, more than 3 million Egyptians have been screened with a plan to screen 30 million in 2018.[10]

In the absence of an effective vaccine, tackling risky practices associated with HCV infection continues to be the primary preventive strategy. Modeling studies proposed that adjoining targeted national preventive and curative interventions might significantly reduce HCV spread and burden in Egypt.[11,12] HCV elimination would not be achievable without prevention.

The World Health Organization (WHO) estimated that reuse of injection equipment accounted for 40% of new HCV infections worldwide in the year 2000.[4,12,13] In Egypt, HCV infection is mainly a healthcare-driven epidemic.[12] Reuse of medical injections contributed to around 40% of prevalent hepatitis C cases and is currently one of the primary risk factors for new HCV infections.[4] Subsequently, the MOHP scaled up efforts for safe injection practices in healthcare facilities. In Egypt, healthcare is provided by public, private, health insurance, and informal sectors. Service providers across these different levels of healthcare are not uniformly trained, and accordingly adherence to safe injection practices may vary widely and monitoring could be challenging, particularly in remote areas. In 2016, two-thirds of providers in private facilities reported removing needles from conventional syringes (CS) by their hands; in governmental facilities the equivalent proportion was also high (40%).[13]

In addition, the level of community awareness is still low. For instance, in rural Egypt most injections are administered in pharmacies after prescription by nonphysicians.[14] Furthermore, many Egyptian patients prefer injectable over oral therapies, assuming that the former are more effective and have faster curative action. This overuse of injections was recently documented in a 2016 MOHP national study, where the average number of injections per person per year was 5.9—almost twice the average global estimate (2.9).[14] It could be expected that this rate of overuse may also contribute to reuse of CS.

The safety-engineered injection syringe (SES) is designed so that after an injection or aspiration, a reuse prevention feature is activated and the syringe cannot be used twice.[13] The WHO recommends using an SES instead of CS for therapeutic injections, particularly in countries where reuse of syringes is common and HCV infection is prevalent.[13] Egypt is a pilot intervention country of WHO's global injection safety campaign. One of the key implementation strategies of the injection safety intervention is conducting cost-effectiveness research on the adoption of the SES.[13] At present, an SES may be more expensive than CS. Depending on the technical complexity of the safety mechanism, an SES may cost the same or 10 times as much as CS ($0.04-$0.4 vs $0.03-$0.04).[13] Nevertheless, the cost of introducing the SES to prevent injection-associated new HCV infections is likely less than the high cost of treating new HCV infections.

The global call to shift to the exclusive use of an SES with reuse prevention features by 2020 will greatly reduce HCV transmission[13] at different levels of the healthcare system. Our objective was to assess the health benefits and aggregated costs of the introduction of the SES as a national preventive strategy over CS from the governmental public healthcare system perspective.

Methods

A cohort Markov process model was developed to project costs and outcomes associated with the adoption of SES versus CS use. This type of modeling study is used for analyzing clinical problems involving measurement of its consequences over time.[15] Figure 1 shows a decision tree and half-cycle–corrected Markov model that simulated the occurrence of HCV infections because of reuse of injection equipment[13,16] within the healthcare settings for a hypothetical cohort of 10 000 patients. The decision tree illustrates the possibility of getting infected, whereas the Markov model focuses on the chronic infection (F3). The National Treatment Program (NTP) for hepatitis C was applied in both strategies.

All cohort individuals entered the model in a healthy state—defined as HCV free. The model cohort was exposed to the risk of HCV infection via unsafe injection practices through a contaminated syringe. The model captured the progression of the individuals who moved to the infected state according to the natural history of hepatitis C, starting the hepatitis C morbidity chain. These individuals either cleared the virus or moved into the chronic stage.

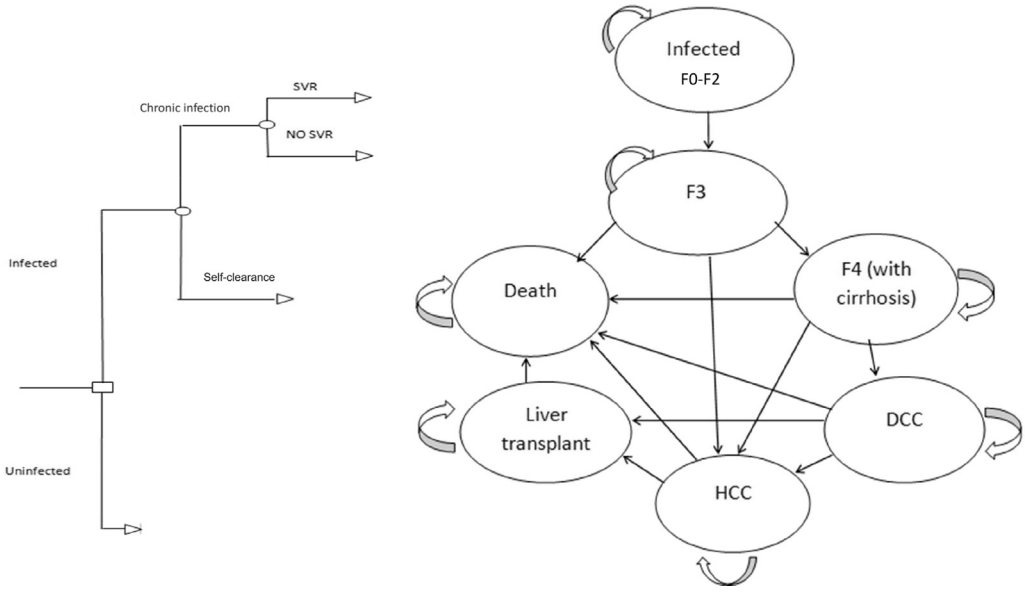

Fig. 1 – Decision tree and Markov model diagram. SVR indicates sustained virological response; F3, fibrosis score; F4, fibrosis score; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

The structure of the model reflects the national treatment practice and relevant disease burden.[6,11,17] The identified health states (ie, model contents) were mostly derived from the literature and then validated by clinical experts. Chronic infected F3 and F4 health states started to get treated with DAAs in the model. A time horizon of 30 years was selected to reflect the long-term outcomes and costs. The cycle length of the model was chosen to be 1 year for an accurate estimation of the timing of health states and related costs.[18]

Data of the model input parameters (Table 1) were collected between September and November 2017.

Clinical Parameters

The following health states were included: infected (defined as patients who were infected with HCV and then resolved the infection); fibrosis score F3 (defined as patients who were infected with HCV without developing cirrhosis); fibrosis score F4 (defined as patients who had been infected with HCV and had cirrhosis); decompensated cirrhosis (DCC; defined as patients who were at high risk of dying from ascites, bleeding varices, encephalopathy, and jaundice); hepatocellular carcinoma (HCC; defined as type of primary liver cancer that develops in patients with chronic liver

Table 1 – Model input parameters and data sources.

Input parameters	Base case	Low value	High value	Data sources
Probability of HCV infection by CS	0.4	0.32	0.48	[16]
Probability of HCV infection by SES	0.014	0.0112	0.0168	[16]
Acute infection to chronic infection	0.75	0.55	0.85	[11,17]
Discount rate	0.035	2	6	[24]
SOF+DAC efficacy	0.954	0.886	0.99	[21]
Transition probabilities				
Infected to F3	0.12	0.109	0.133	[19]
F3 to F4	0.116	0.104	0.129	[19]
F3 to HCC	0.001	0	0	[20]
F3 to death	0.079	0.06	0.1	[20]
F4 to DCC	0.039	0.01	0.079	[42]
F4 to HCC	0.014	0.01	0.079	[42]
F4 to death	0.054	0.039	0.074	[43]
DCC to HCC	0.005	0.002	0.013	[44]
DCC to LT	0.05	0.04	0.06	[45]
DCC to liver-related death (1st year)	0.182	0.065	0.19	[44]
DCC to liver-related death (year 2+)	0.112	0.065	0.19	[44]
HCC to LT	0.015	0.12	0.18	[45]
HCC to death (1st year)	0.707	0.43	0.77	[17,46]
HCC to death (year 2+)	0.162	0.11	0.23	[17,46]
LT to liver-related death (1st year)	0.14	0.107	0.331	[17,45,47]
LT to liver-related death (year 2+)	0.048	0.039	0.6	[17,45,47]
Utilities				
Infected utility	0.87	0.83	0.9	[48]
F3 utility	0.71	0.64	0.8	[48]
F4 utility	0.71	0.64	0.8	[48]
DCC utility	0.66	0.57	0.73	[48]
HCC utility	0.56	0.51	0.6	[48]
LT utility	0.65	0.59	0.72	[49]
Post LT utility	0.83	0.64	1	[49]
Increment utility of achieving SVR	0.05	0.02	0.05	[48]
Costs (USD)				
Number of injections per person per year	5.9	4.72	7.08	[14]
Infected cost	233	187	280	Oral communication, December 15, 2017
F3 cost	1574	1260	1890	Oral communication, December 15, 2017
F4 cost	1888	1511	2266	Oral communication, December 15, 2017
DCC cost	8591	6873	10 310	Oral communication, December 15, 2017
HCC cost	12 106	9685	14 528	Oral communication, December 15, 2017
LT cost	98 425	78 740	118 110	Oral communication, December 15, 2017
Post LT cost	11 811	9 449	14 173	Oral communication, December 15, 2017
Cost of treatment course (SOF+DAC)	585	469	703	Oral communication, December 15, 2017
Monitoring cost	288	231	346	Oral communication, December 15, 2017
Treatment initiation cost	233	187	280	Oral communication, December 15, 2017
Annual total cost / year 2	369	295	442	Oral communication, December 15, 2017
Cost of CS (one syringe)	0.035	0.03	0.04	Oral communication, December 15, 2017
Cost of SES (one syringe)	0.22	0.04	0.4	[13]

CS indicates conventional syringes; DCC, decompensated cirrhosis; DCV, daclatasvir; F3, fibrosis score; F4, fibrosis score; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SES, safety-engineered syringes; SOF, sofosbuvir; SVR, sustained virologic response; USD, US dollar.

disease); liver transplantation (LT; defined as patients who had undergone liver replacement because of life-threatening decompensated complications); and death (defined as death from any cause).

All model inputs are described in Table 1. Transition probabilities for HCV natural history patients with and without sustained virological response (SVR) were derived from meta-analysis of 111 studies of individuals with chronic HCV infection (n = 33 121)[19] and a decision-analytic model in adults with chronic HCV genotype 1 and compensated liver disease in phase III, randomized, double-blinded, multicenter trials ADVANCE (1095 treatment-naive patients) and REALIZE (833 relapsers, partial responders, and null responders).[20] In real-world settings, the efficacy of sofosbuvir and daclatasvir (with or without ribavirin) treatment regimen, defined as SVR at week 12 after treatment, was obtained from Egypt's NTP data prospectively collected from 18 378 viremic patients with chronic HCV infection, mostly genotype 4.[21]

Outcomes

Quality-adjusted life-years (QALYs) were evaluated for each strategy. The utility value of infected, F3, F4, DCC, HCC, LT, and post-LT health states was obtained from a study that measures the HCV-infected patients' utility using different methods: the SF-12 questionnaire culturally adapted to Egypt, a rating scale using a visual analog scale, and the time trade-off method.[22]

Costs

The costs of introducing SESs per year were calculated as the number of injections per person per year multiplied by the global SES price range. The base-case cost of SESs and CS was derived from the average value of $0.04-$0.4 and $0.03-$0.04, respectively. The resources required for the SES and CS waste collection and management were not taken into account because of lack of data; similarly, resources required for training on SES use were not considered because they would be provided by the syringes manufacturers. We used a secondary data approach for the model from cost data sets to generate cost inputs. The direct medical costs of HCV were obtained from the National Liver Institute and the MOHP (Table 1). Drug costs for the management of each complication in the model were based on Egyptian treatment practice. The purchasing power parity rate was used to convert the local currency to US dollars.[23] All costs in the tables and results were reported in US dollars for the financial year of 2017. All costs and health effects were discounted at 3.5% annually.[24]

Model Assumptions

Some reasonable assumptions were incorporated in this study. First, we assumed that HCV-infected patients who achieved SVR after therapy did not continue to develop cirrhosis, DCC, or LT because the risk of liver failure and hepatic decompensation after achieving SVR is very low, and thus no long-term monitoring is necessary.[25,26] Second, those who were not infected with HCV in both SES and CS groups at index did not incur any costs and had full health. Third, we did not include other infection risks, such as HBV, HIV, and other bloodborne diseases into the model because those were outside the scope of this study. Fourth, we did not include the possibility of reinfection because this decision model is a static one.

Sensitivity Analyses

One-way sensitivity analyses were performed to test the robustness of our results across the variations in input model parameters.[27] The stability of the model to different model structures and assumptions was tested with univariate sensitivity analyses of clinical parameter estimates and costs of health states. The robustness of the model to changes in health state utilities within plausible ranges determined from different published sources was also explored.[22,28,29] Monte Carlo simulation was conducted to perform a stochastic uncertainty analysis of the probability that the SES represents a cost-effective use of resources given a specified budget constraint. All analyses were performed using Microsoft Excel 2010.

Results

The use of SES demonstrated a reduction in the burden of injection-associated HCV infection because of unsafe practices in Egypt, which translated into improved quality of life, measured in QALYs. In patients who were exposed to previously used syringes, the probability of HCV infection was 1.4% in the SES group and 40% in the CS group. Adoption of the SES use policy averted 177 HCV cases and 157 HCV-related deaths per 10 000 individuals over a time horizon of 30 years. The base-case results for the two arms modeled are shown in Table 2.

The estimate of total QALYs gained per person while using SES was 9.48 compared with 8.53 for the use of CS (difference; 0.95 QALYs). The total costs per person for using SES and CS were $62 and $1774, respectively. The difference in costs was $−1712. These SES costs when compared with the use of CS yielded an incremental cost-effectiveness ratio (ICER) of $−1802 per QALY gained for the use of SES (Table 2). The adoption of SES is the dominant option (less costly and more effective) in reduction of injection-associated HCV infection than the use of CS. Thus, introducing the SES as a prevention strategy is the cost-saving option; preventing 177 HCV cases in SES cohort results in a cost saving of $1712 per case and is a more effective option (better quality of life) than the use of CS in Egyptian settings.

Sensitivity Analyses

The base-case analysis of this model used the average costs for the National Liver Institute and the MOHP. Sensitivity analyses using the uncertainty ranges estimated from the lowest and highest cost values for the above databases did not alter the drawn conclusions. Adoption decision was not significantly affected by other values over their reasonable ranges (Table 1).

Table 2 – Results of cost-effectiveness analysis of two injection strategies in Egypt over 30 years.

Strategy	Total costs per person (USD)	QALY gained per person	ICER	Interpretation
SES	62	9.48	$−1802	Dominant strategy
CS	1774	8.53		Base line comparator
Difference	−1712	0.95		

CS indicates conventional syringes; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SES, safety-engineered syringes; USD, US dollar.

One-way sensitivity analyses (Fig. 2) indicated that the F3 utility had the greatest effects on the results when comparing adoption of SES to use of CS, whereas the least sensitive factor was the transition probability from DCC to liver-related death in the second year.

In addition, a stochastic uncertainty analysis was conducted. All of the variables were simultaneously varied within various error distributions over 1000 iterations. They are depicted in the cost-effectiveness plane scatter plot and cost-effectiveness acceptability curve shown in Figures 3 and 4, respectively.

Discussion

In the current study, adoption of the SES use would avert 177 HCV infections and 157 HCV-related deaths per 10 000 individuals. The estimate of total QALYs gained per person while using an SES was 9.4 compared with 8.5 for the use of CS. In addition, there was substantial cost savings per person: $−1712 over a time horizon of 30 years based on the number of injections per person per year. The QALY gain for SES use could be attributed to the number of HCV infections and HCV-related deaths averted and high efficacy of the newly adopted DAAs with ≥95% SVR 12 weeks after treatment.[30,31]

The estimated global burden of disease attributable to unsafe injection practices in 2000-2030 is 9.2 million disability-adjusted life-years (DALYs).[32] The WHO estimated that the cost-effectiveness ratio for national policies for the safe and appropriate use of injections is $102/DALY averted.[13] There are few published studies on cost-effectiveness of safety-engineered devices in healthcare settings. Moreover, there is currently no existing research studies from LMICs. Dziekan et al modeled the cost-effectiveness of policies for the safe use of injections in 10 global epidemiological subregions in terms of cost per DALY averted.[16] The average incremental cost-effectiveness ratio for interventions to reduce injection use in the Eastern Mediterranean Region was $400/DALY averted.[16]

Other systematic reviews investigating SES use focused on the prevention of accidental needle-stick injuries (NSIs) in healthcare workers (HCWs).[33-36] It was concluded that there is moderate-quality evidence that the use of safety-engineered devices reduces NSI rates among HCWs.[33,34] The WHO reported that NSIs were encountered by more than 2 million HCWs annually, accounting for 37.6%, 39%, and 4.4% of hepatitis B, hepatitis C, and HIV/AIDS cases among HCWs, respectively.[37] There are greater health benefits expected in settings with higher HIV, HBV, and HCV disease prevalence; higher sharps injury; and higher injection reuse rates.[13] Notably, NSIs among HCWs in LMICs are at least twice the number reported in developed countries[38]; two-fifths of them occur during blood drawing.[39] SES may also be a useful harm-reduction policy in people who inject drugs.[13]

In Egypt, unsafe injection practices continue to occur because of lack of monitoring and evaluation.[14] Raising awareness and patient education are key to create a community demand for safe injections. Simultaneously, reducing unnecessary injections is an urgent and critical strategy.[40] In LMICs, the average number of injections per person per year decreased by 15% from 2000 to 2010 (from 3.4 to 2.9),[40] but it is still higher in Egypt (around 5.9).[14] Most injections were administered for therapeutic indications, and a considerable proportion could be replaced by oral forms.[14] Medical training of physicians should reinforce the importance of limiting the prescription of injectable medications, unless absolutely necessary. Nevertheless, this may be challenging in Egypt, where injections are prescribed and delivered not only by physicians but also by other nonmedically trained personnel.[14]

On the other hand, Breban and colleagues' mathematical model assessed the effect of public health interventions on HCV spread in Egypt combining both reductions in unsafe injections with treatment of infected individuals.[12] Their model identified individuals with high rates of medical injections (more than 10 per year) as responsible for the spread of HCV in Egypt.[12] Targeting these individuals with preventive or curative interventions would have a much greater effect on HCV spread than would untargeted interventions, thus decreasing the basic reproduction number below one.[12] SES use will augment this positive effect. During their lifetime, one infected individual is likely to infect 3-4 people; thus averting 1 case would avert infection of 4 people. Also, Waked and colleagues' projections show that if preventive measures are not

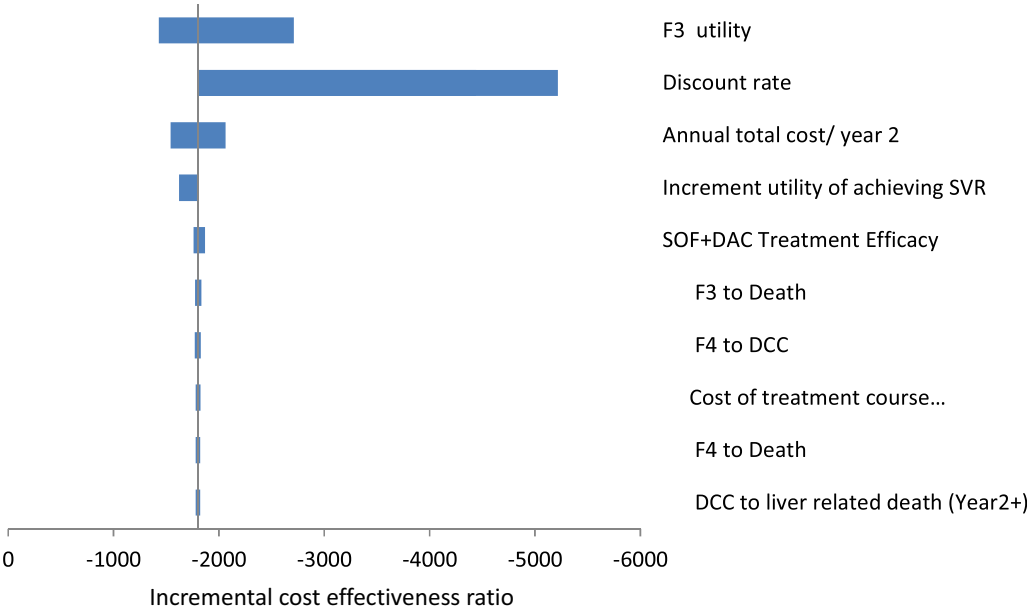

Fig. 2 – Tornado diagram describing one-way sensitivity analyses. SVR indicates sustained virological response; F3, fibrosis score; F4, fibrosis score; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SOF, sofusbovir; DCV, daclatasvir.

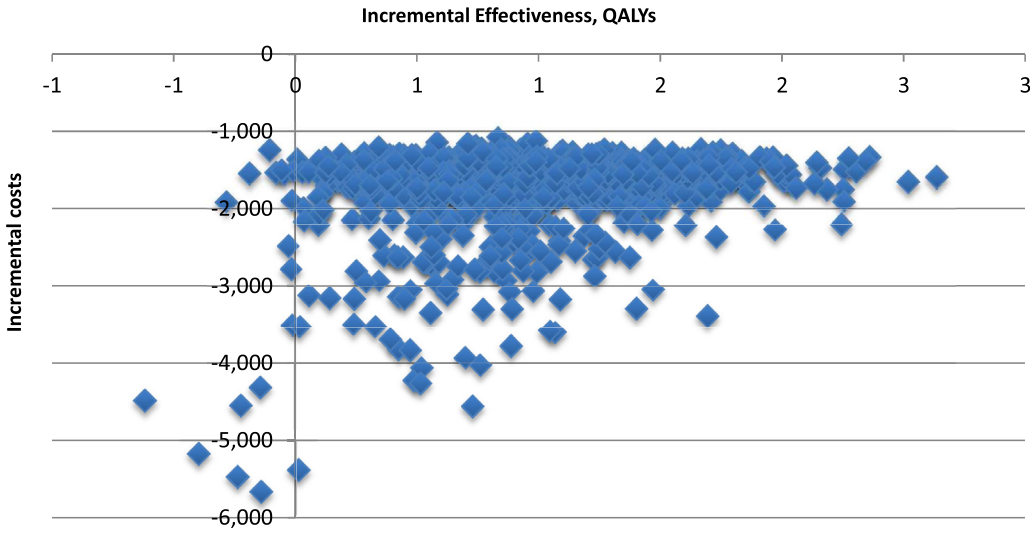

Fig. 3 – Incremental cost-effectiveness plane for safety-engineered syringes versus conventional syringes. QALY indicates quality-adjusted life year.

effectively undertaken together with the current NTP, a million more cases will accumulate by 2030 and hepatitis C elimination would not be achievable. [9]

The present study is the first economic evaluation that addresses both the economic and the clinical implications of safe injection practices as a preventive intervention from a governmental healthcare system perspective, especially in a country with a high burden of HCV infection such as Egypt. Additionally, data for input parameters were derived from meta-analysis of 111 studies identified by a systematic unbiased literature search and from a representative national treatment center, where the target population may be treated. Furthermore, the approach applied could be replicated in other resource-constrained countries and for other injection-associated infections.

In various sensitivity analyses, the incremental costs and outcomes even at the lowest and highest estimates of all parameters in the model still favor introducing the SES use policy over the CS use as a preventive strategy.

The present cost-effectiveness analysis encountered some limitations. First, it did not include cost of waste management and training on SES because of unavailability of data. It should include the cost of implementation (training HCWs, follow-up of needlestick injuries, and waste management) and the cost of the devices themselves.[13] Nevertheless, it is expected that SES use policy will be even more cost saving with the foreseen technology transfer for manufacturing SES, which can further decrease the cost in the long-term. It is projected that market forces and increased community demand would have an impact on pricing because economies of scale and competition will lower the price per unit.

Second, direct nonmedical costs and indirect costs from a societal or patient perspective were not included because of the unavailability of national data; such costs would have led to further cost savings. These costs would be of substantial importance because up to 60% of expenditure on health in Egypt is out of pocket, whereas national insurance coverage is 51%.[41] Employing

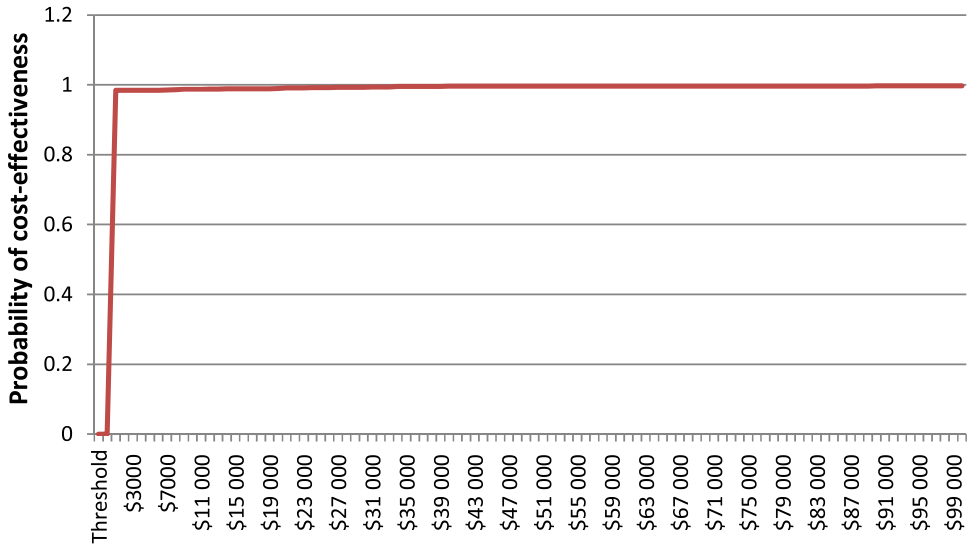

Fig. 4 – Cost-effectiveness acceptability curve for safety-engineered syringes versus conventional syringes.

the societal or patient perspective might thus significantly favor the SES use as a preventive measure over CS. Moreover, the current price ranges of SES—which vary from the least to the most technically complex mechanism—will soon decrease as the recent technology transfer materializes into production of the highest edge of SES at a much lower cost per unit in Egypt.

Third, the model was restricted to HCV infection associated with unsafe injection practices and excluded other infections possibly transmitted through contaminated syringes (eg, HBV and HIV) because of scarcity of relevant data. Therefore, extending the analysis to include these bloodborne diseases might evaluate the full impact of the effectiveness of SES as a preventive measure for HCV, HBV, and HIV in Egypt. Fourth, screening of HCV patients was limited to F3 and F4 because only those patients were covered by the governmental sector, whereas F0 to F2 are covered by other supported programs.

Our model is static and thus did not consider the longer-term kinetic impact of the possible reduction in HCV transmission because of waning of the cohort effect in the aging population infected during the historic mass campaign of antischistosomial therapy and the possibility of re-infection. Also, other synergistic interventions such as increased awareness about HCV modes of transmission and the long-term effect of DAA treatment on the viremic reservoir could underestimate the cost-effectiveness of SES use. In addition, we considered only patients treated under the NTP because this study is investigating the cost-effectiveness of the alternative strategy from a governmental perspective. Therefore, the lack of accurate data regarding the number of treated patients in the private sector may be of concern, especially with the continuous reduction of treatment prices and the growing number of patients who seek treatment outside the NTP.

Conclusions

Adoption of SES in the Egyptian healthcare settings is a cost-saving strategy. Our results are consistent with the WHO Injection Safety Program and Safe Injection Global Network initiatives, which call for adoption of smart syringes. The introduction of SES as one of the most urgently needed interventions is encouraged to decrease HCV burden in similar LMIC settings. The use of SES as a prevention strategy may bring substantial population-level health gains and governmental cost savings in developing countries. Policies for safe and appropriate use of injections are natural additions to ongoing robust and ambitious efforts in HCV treatment and complementary to other preventive and awareness-based approaches.

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Competing Interests

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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