Return on Investment from the Prevention of Spinal Muscular Atrophy in Kuwait

Salem M. Abuhadida [1]* 🆔

[1] Health Economics Unit, Ministry of Health, KUWAIT
*Corresponding Author: sabuhadida@moh.gov.kw

ARTICLE INFO	ABSTRACT
Received: 4 Jun. 2022 Accepted: 3 Jul. 2022	**Background**: Spinal muscular atrophy (SMA) is a rare genetic disease with a devastating nature and associated with significant clinical and economic burden. Fortunately, the availability of genetic screening and prevention technologies made preventive strategy possible. The aim of this study is to assess the return on investment from a prevention program that includes premarital genetic screening, preimplantation genetic diagnosis, and in vitro fertilization pertaining to SMA, spanning five-year period from the financial perspective of the Ministry of Health (MOH) in Kuwait. **Methods**: A stochastic financial model was developed following a return on investment (ROI) approach spanning five-year period. **Results**: An average ROI estimated to be 11% with cost saving amounted to 466,159 KWD (1,524,339 USD). The financial burden if the prevention program was not implemented is 16,441,539 KWD (53,763,832 USD). **Conclusion**: This study is one of the very few in the region to estimate the benefits of implementing a prevention program pertaining to SMA from the financial perspective of the MOH in Kuwait. **Keywords:** zolgensma, premarital genetic screening, preimplantation genetic diagnosis, in vitro fertilization, stochastic financial model

INTRODUCTION

Spinal muscular atrophy (SMA) is a devastating rare genetic disease with poor prognosis, which follows an autosomal recessive mode of inheritance, requiring both parents to be a carrier of the SMA1 defective gene in order to pass the disease to their offspring (Kolb and Kissel, 2015). In the year 2019, the Food and Drug Administration (FDA) approved a single shot gene therapy onasemnogene abeparvovec (zolgensma) for the treatment of less than two years of age pediatric patients with bi-allelic defective SMA1 gene (US Food and Drug Administration, 2019). It has been the most expensive drug in the market costing 2.1 million United States dollars (Broekhoff et al., 2021).

The high cost led the National Institute for Clinical Excellence in the United Kingdom into two years of ongoing economic evaluation before it made the drug accessible to the affected patients under public pressure (Nuijten, 2021). Kuwait provides universally free healthcare to its citizens and was the second country in the world to make this drug accessible to patients without charges. Beside the cost of gene therapy there are the direct medical costs incurred by Intensive Care Unit admissions with mechanical ventilation support, frequent hospital visits, corrective surgeries among other treatment modalities (Armstrong et al., 2016). Such disease can burden the healthcare system financially and imposes a significant impact on constrained healthcare resources.

Amid attesting to this significant problem, a glimpse of hope exists through an evidence based preventive program. A premarital genetic screening (PMS) to detect the defective gene carriers followed by preimplantation genetic diagnosis (PGD) to identify healthy gametes (male sperm or female ovum) and in vitro fertilization (IVF) offers a viable path to a healthy offspring (Gyngell et al., 2020). Currently in Kuwait, blood screening for infectious diseases and inherited blood disorders at the premarital clinic in the Ministry of Health (MOH) is required for obtaining a marriage license and mandated by legislation (Rouh AlDeen et al., 2021). In this study the aim is to assess the return on investment (ROI) from a prevention program that includes PMS, PGD and IVF pertaining to SMA, spanning five-year period from the financial perspective of the MOH in Kuwait.

Table 1. Projected number of applicants

Year	Projection	First partner screen	Additional screening	Total
2023	26,732	13,366	668	14,034
2024	26,975	13,488	674	14,162
2025	27,221	13,611	681	14,292
2026	27,468	13,734	687	14,421
2027	27,718	13,859	693	14,552

Table 2. Model parameters

Parameter	Distribution	Values (α, β)
Number of applicants annually	Uniform	14,034-15,000
Unit cost of premarital screen	Gamma	83.3 (43.9, 1.9)
Unit cost of preimplantation genetic diagnosis and in vitro fertilization	Gamma	3,833.3 (13.6, 282.6)
Cost of spinal muscular atrophy	Gamma	657,834.2 (378.5, 1738)
Discount rate	Beta	3% (8.7, 281.3)
Number of prevented cases annually	Uniform	1-3
Total number of cases annually	Uniform	3-7

METHODS

A stochastic financial model was developed in Excel version 16.54, following an ROI approach spanning five-year period. Benefits (positive discounted cash flows) are the averted direct medical costs of SMA prevented cases, while costs (negative discounted cash flows) are the costs incurred from the PMS, PGD, and IVF. Cost saving results from the sum of benefits after taking away the sum of costs, while ROI is the percentage ratio of the cost saving to the sum of costs. Furthermore, financial burden was estimated as the total direct medical costs of SMA cases if the program was not implemented.

Prevention Program

The screening strategy requires one partner to be screened for carrier state. If the tested partner is negative or if one of the partners is negative, there is no chance the couple will pass the disease to their offspring. As a result, if the tested partner was positive then the other one must be tested. If both were tested positive, then they are advised to go through genetic counseling, PGD and IVF. Historical data from 2010 to 2019 for the annual number of applicants screened at the premarital screening center in MOH were obtained from a Kuwaiti report (Rouh AlDeen et al., 2021) and was used to project the number of applications for five years from 2023 to 2027 based on exponential population growth (Schacht, 1980) using the following formula:

$$P = P_o \times e^{RT},$$

where P is the total population after time "T" in years, Po is the starting population, R is the rate of growth in percent, T is the time in years, and e is the Euler number (2.71828).

The number of additional screening when the tested partner is positive was estimated following one of the highest reported SMA carrier frequency rate in the literature which is 1/20 (Shawky and El-Sayed, 2011). The results show that the total number to be screened ranged from 14,034 to 14,552 over five years in **Table 1**.

However, a wider range will be assumed arbitrarily in the model ranging from 14,034 to 15,000 as shown in **Table 2**.

The cost of screening per unit for a SMA carrier state in a single panel was obtained by inquiries from the private sector since the fact that screening has not yet been implemented in the MOH. While the costs of genetic counselling, PGD and IVF obtained from Abuhadida et al. (2022).

Epidemiology and Costs of SMA

The costs of SMA were obtained from a previous orphan diseases study (Abuhadida et al., 2022) and included the gene therapy, pediatric intensive care admissions, emergency room visits, corrective surgeries and other medical supports. While the number of annual cases of SMA was reported by experts' opinions in national genetic laboratory of Kuwait Medical Genetic Center from the aforementioned study. The discount rate is 3% in accordance with World Health Organization (WHO) recommendations for public health interventions (Bertram et al., 2021).

Sensitivity Analysis

This study assumed a pessimistic scenario where only half or less than half of the cases are prevented through the program annually. All the parameters or inputs in the model are shown in **Table 2**.

A univariate sensitivity analysis was performed to assess the impact of each parameter on ROI. In addition, the model is made stochastic reflecting a multivariate probabilistic sensitivity analysis where all parameters are given a probability distribution. A gamma distribution was assigned for costs because they are known to be rightly skewed with positive values (Cantoni and Rochetti, 2006).

A beta distribution was assigned for discount ratebecause values are bounded between 0 and 1 (Hu et al., 2020). A uniform discrete distribution was assigned for parameters that do not exhibit particular probability distribution. A Monte Carlo simulation was performed with 10,000 iterations and probabilistic averages and their distributions were estimated for amount of cost saving, ROI and financial burden. Results are reported in Kuwaiti Dinars (KWD) and in United Sates Dollars (USD) with an exchange rate of 1 KWD equivalent to 3.27 USD dated April 22nd 2022 (https://www.xe.com/).
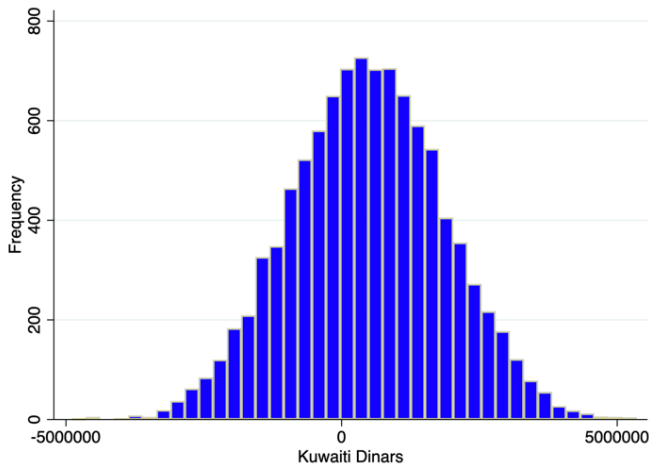
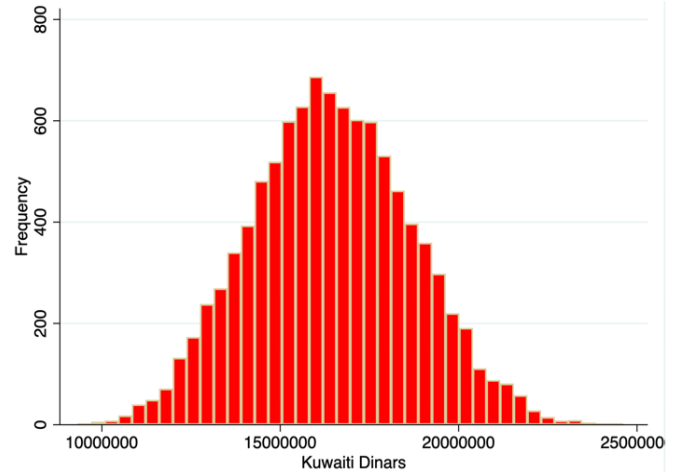**Figure 1.** Monte Carlo simulation for cost saving

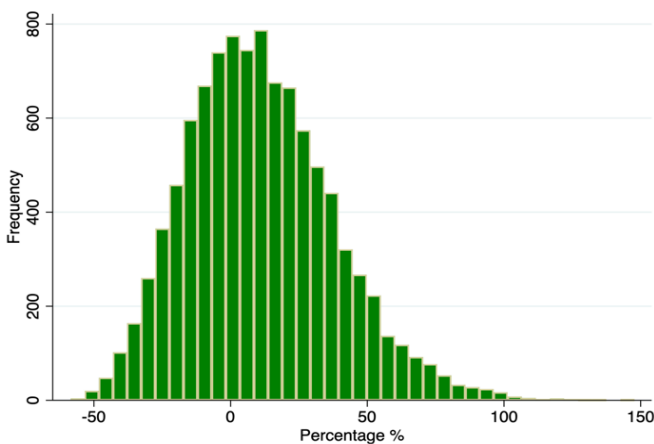**Figure 3.** Monte Carlo simulation for financial burden

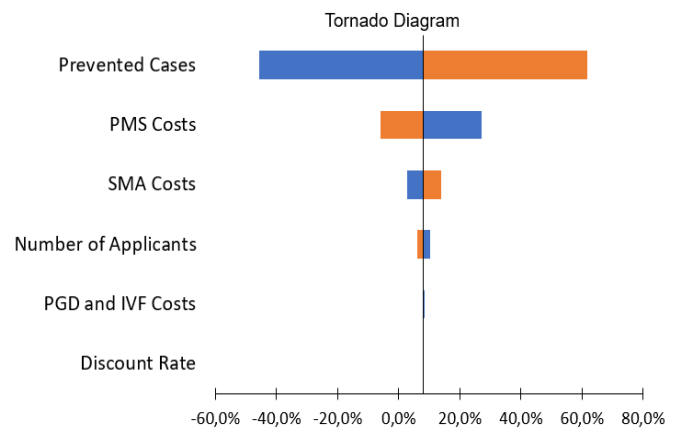**Figure 2.** Monte Carlo simulation for ROI

Figure 4. Univariate sensitivity analysis for ROI

RESULTS

Over five-year-period, the average cost saving amounted to 466,159 KWD (1,524,339 USD), the median 471,869 KWD (1,543,011 USD) and distribution shown in **Figure 1**.

The average ROI expected to be 11%, the median 9% and distribution shown in **Figure 2**. The probability of achieving a positive ROI is 63%.

The average financial burden in case the MOH did not implement the prevention program is expected to be 16,441,539 KWD (53,763,832 USD), the median 16,391,473 KWD (53,600,116 USD) and distribution shown in **Figure 3**.

Meanwhile, univariate sensitivity analysis in **Figure 4**, shows that the number of prevented cases had the most impact on the ROI, followed by the costs of PMS, SMA costs, number of applicants, and lastly PGD and IVF costs.

DISCUSSION

The result of the study is very encouraging and leave no doubts about the benefits of implementing such program at least from the financial perspective and budget constraint.

The model has several strengths. Firstly, the stochastic nature of the financial model gives it a robustness especially from uncertainties inherent in the acquired data. Secondly, as seen from the univariate sensitivity analysis, the number of cases prevented had the most impact on the results, meanwhile the model follows a pessimistic scenario where only 50% or less of the cases were prevented, yet the results had high probability of being cost saving. The pessimistic scenario is also supported by a previous study in the premarital screening center in MOH showing that PMS and genetic counselling was effective in preventing 50% of the cases of Thalassemia disease (Rouh AlDeen et al., 2021). Thirdly, in the prevention strategy, the numbers screened in the model were slightly higher than the projected ones even though they were estimated on the highest reported carrier frequency of 1/20 (Shawky and El-Sayed, 2011) while worldwide the reported carrier frequency ranged between 1/40 to 1/60 (Prior and Professional Practice and Guidelines Committee, 2008). Fourthly, the screening costs are likely to be overestimated because they were obtained from the private sector in Kuwait. Meanwhile, the unit cost of screening was estimated in the MOH to be around 33 KD for the first year and depreciating further over five years. It is safer from the financial risk management perspective to overestimate than underestimate acquisition costs. Lastly but not least, the study has short duration running over five years, unlike most economic evaluation studies which assume lifetime costs and benefits without paying attention to possibilities of technological innovation or disruptions.

The model has several limitations. Firstly, the high cost of SMA disease is attributed mainly to the gene therapy cost and excluding this cost will not make the result cost saving. In that case, an economic evaluation such as cost-utility analysis (CUA) maybe warranted. The reason for this is that CUA incorporated the values of health benefits of prevention such as quality adjusted life years (QALYs) in the model (Robinson, 1993). QALYs can add further value to the model in two ways, either making the model cost-effective or converting QALYs into monetary value through willingness to pay per QALYs (Johannesson and O'Conor, 1997). Subsequently, the previous point does lead us to the second limitation of not incorporating health benefits such as QALYs or other psychological and emotional factors in the model. Adding these factors will reinforce our results. However, it was intentional not to include these for several reasons. Firstly, the concept of QALYS or social value is not universally approved and less understood from the perspective of policy makers and healthcare leaders (National Council on Disability, 2019; Partnership to Improve Patient Care, 2017; Pioneer Institute, 2020) unlike direct medical costs which are more tangible and directly related to budget constraints. Secondly, faith in the valuation of these factors maybe be lost once leaders become familiarized about the inconsistencies resulting from using different valuation methods used to estimate these factors (Mulhern et al., 2014, 2016; Xie et al., 2014). The aforementioned estimations together will add a second layer of uncertainties to this study, which is quite unnecessary since the result is already highly cost saving without adding such factors. More importantly, healthcare costs, access to drugs and screening strategy is unique to each country. Each country needs to assess their own prevention strategy. Moreover, within each country as changes in costs and technological disruption continue to happen, these strategies need to be re-evaluated in the light of the new emerging scenarios.

Ironically the WHO encourages governments to spends billions of dollars to prevent metabolic diseases such as obesity, diabetes, cardiovascular and respiratory diseases (Elmusharaf et al., 2021), which are multifactorial behavioral diseases known to be difficult to control (Schwarz et al., 2007) and associated with unavoidable risks pertaining to chemical and air pollutions in the environment (Clementi et al., 2019; Le Magueresse-Battistoni et al., 2018). On the other hand, little efforts have been done to prevent SMA and other genetic diseases which can be prevented at a high scale and a fraction cost.

One of the crucial challenges to the applications of genomic medicine and national genetic screening is the ethical dilemma associated with population-based screening. Given the severe morbidity and mortality nature of this disease and the availability of screening and prevention technologies, calls have been made by the American College of Medical Genetics for population-based screening for SMA carrier state since 2008 (Prior and Professional Practice and Guidelines Committee, 2008). Several other countries have already conducted population-based screening for SMA (Verhaart et al., 2017). From the medical ethics point of view, the moral pillars of autonomy, beneficence and justice do support the using of population-based screening and prevention of SMA (Gyngell et al., 2020). Next to the MOH approval is Kuwaiti Parliament which is the legislature assigned to approve the addition of SMA genetic screening to the existing screening tests in the premarital clinic.

Lastly but not least, for a successful program it is essential for Kuwait Medical Genetic Center to monitor the number of SMA cases annually to assess the effectiveness of the program from real world data perspective.

CONCLUSION

This study is one of the very few studies regionally to address the financial benefits from the prevention of SMA. The results show that over five years, the prevention program has high probability of positive returns with an average ROI of 11% and a cost saving amounted to 466,159 KWD (1,524,339 USD). Furthermore, not implementing the program could impose a significant financial burden on MOH amounted to 16,441,539 KWD (53,763,832 USD). The MOH in Kuwait is highly advised to implement the prevention program and monitor its effectiveness.

REFERENCES

Abuhadida, S., Bastaki, L., Bash, B. and Alhindal, B. (2022). Return on investment from the prevention of orphan diseases in Kuwait. *Annals of Public Health*. https://doi.org/10.55085/aph.2022.637

Armstrong, E. P., Malone, D. C., Yeh, W. S., Dahl, G. J., Lee, R. L. and Sicignano, N. (2016). The economic burden of spinal muscular atrophy. *Journal of Medical Economics*, 19(8), 822-826. https://doi.org/10.1080/13696998.2016.1198355

Bertram, M. Y., Lauer, J. A., Stenberg, K. and Edejer, T. (2021). Methods for the economic evaluation of health care interventions for priority setting in the health system: An update from WHO CHOICE. *International Journal of Health Policy and Management*, 10(11), 673-677. https://doi.org/10.34172/ijhpm.2020.244

Broekhoff, T. F., Sweegers, C., Krijkamp, E. M., et al. (2021). Early cost-effectiveness of onasemnogene abeparvovec-xioi (zolgensma) and nusinersen (spinraza) treatment for spinal muscular atrophy I in The Netherlands with relapse scenarios. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 24(6), 759-769. https://doi.org/10.1016/j.jval.2020.09.021

Cantoni, E. and Ronchetti, E. (2006). A robust approach for skewed and heavy-tailed outcomes in the analysis of health care expenditures. *Journal of Health Economics*, 25(2), 198-213. https://doi.org/10.1016/j.jhealeco.2005.04.010

Clementi, E. A., Talusan, A., Vaidyanathan, S., Veerappan, A., Mikhail, M., Ostrofsky, D., Crowley, G., Kim, J. S., Kwon, S. and Nolan, A. (2019). Metabolic syndrome and air pollution: A narrative review of their cardiopulmonary effects. *Toxics*, 7(1), 6. https://doi.org/10.3390/toxics7010006

Elmusharaf, K., Grafton, D., Jung, J. S., Roberts, E., et al. (2022). The case for investing in the prevention and control of non-communicable diseases in the six countries of the Gulf Cooperation Council: An economic evaluation. *BMJ Global Health*, 7(6), e008670. https://doi.org/10.1136/bmjgh-2022-008670

Gyngell, C., Stark, Z. and Savulescu, J. (2020). Drugs, genes and screens: The ethics of preventing and treating spinal muscular atrophy. *Bioethics*, 34(5), 493-501. https://doi.org/10.1111/bioe.12695

Hu, C., Zhou, H. and Sharma, A. (2020). Applying beta distribution in analyzing bounded outcome score data. *The AAPS Journal*, 22(3), 61. https://doi.org/10.1208/s12248-020-00441-4

Johannesson, M. and O'Conor, R. M. (1997). Cost-utility analysis from a societal perspective. *Health Policy*, 39(3), 241-253. https://doi.org/10.1016/s0168-8510(96)00878-0

Kolb, S. J. and Kissel, J. T. (2015). Spinal muscular atrophy. *Neurologic Clinics*, 33(4), 831-846. https://doi.org/10.1016/j.ncl.2015.07.004

Kuwait Times. (2019). *SMA patients in Kuwait provided with world's most expensive drug*. Available at: https://storage.kuwaittimes.com/pdf/2019/nov/05/p01.pdf (Accessed 4 June 2022).

Le Magueresse-Battistoni, B., Vidal, H. and Naville, D. (2018). Environmental pollutants and metabolic disorders: The multi-exposure scenario of life. *Frontiers in Endocrinology*, 9, 582. https://doi.org/10.3389/fendo.2018.00582

Mulhern, B., Bansback, N., Brazier, J., Buckingham, K., et al. (2014). Preparatory study for the revaluation of the EQ-5D tariff: Methodology report. *Health Technology Assessment*, 18(12), vii-191. https://doi.org/10.3310/hta18120

Mulhern, B., Shah, K., Janssen, M. F., Longworth, L. and Ibbotson, R. (2016). Valuing health using time trade-off and discrete choice experiment methods: Does dimension order impact on health state values? *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 19(2), 210-217. https://doi.org/10.1016/j.jval.2015.11.005

National Council on Disability. (2019). *"Quality adjusted life years and the devaluation of life with disability" report*. Available at: https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf (Accessed 4 June 2022).

Nuijten, M. (2021). Pricing zolgensma–the world's most expensive drug. *Journal of Market Access & Health Policy*, 10(1), 2022353. https://doi.org/10.1080/20016689.2021.2022353

Partnership to Improve Patient Care. (2017). *Uses and misuses of the QALY: Ethical issues with qalys and alternative measures of value*. Available at: http://www.pipcpatients.org/uploads/1/2/9/0/12902828/pipc_summary_-_uses_and_misuses_of_the_qaly.pdf (Accessed 4 June 2022).

Pioneer Institute. (2020). *Quality adjusted life years (QALY): The threat to older Americans*. Available at: https://pioneerinstitute.org/wp-content/uploads/dlm_uploads/QALYcovid-PB.pdf (Accessed 4 June 2022).

Prior, T. W. and Professional Practice and Guidelines Committee. (2008). Carrier screening for spinal muscular atrophy. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 10(11), 840-842. https://doi.org/10.1097/GIM.0b013e318188d069

Robinson, R. (1993). Cost-utility analysis. *BMJ*, 307(6908), 859-862. https://doi.org/10.1136/bmj.307.6908.859

Rouh AlDeen, N., Osman, A. A., Alhabashi, M. J., Al Khaldi, R., et al. (2021). The prevalence of β-thalassemia and other hemoglobinopathies in Kuwaiti premarital screening program: An 11-year experience. *Journal of Personalized Medicine*, 11(10), 980. https://doi.org/10.3390/jpm11100980

Schacht, R. M. (1980). Two models of population growth. *American Anthropologist*, 82(4), 782-798. https://doi.org/10.1525/aa.1980.82.4.02a00040

Schwarz, P. E., Reimann, M., Li, J., Bergmann, A., Licinio, J., Wong, M. L. and Bornstein, S. R. (2007). The metabolic syndrome–a global challenge for prevention. *Hormone and Metabolic Research=Hormon-und Stoffwechselforschung=Hormones et metabolisme*, 39(11), 777-780. https://doi.org/10.1055/s-2007-990312

Shawky, R. M. and El-Sayed, N. S. (2011). Clinico-epidemiologic characteristics of spinal muscular atrophy among Egyptians. *Egyptian Journal of Medical Human Genetics*, 12(1), 25-30. https://doi.org/10.1016/j.ejmhg.2011.02.015

US Food and Drug Administration. (2019). *Package insert–zolgensma*. Available aT: https://www.fda.gov/media/126109/download (Accessed 4 June 2022).

Verhaart, I., Robertson, A., Wilson, I. J., Aartsma-Rus, A., et al. (2017). Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy–a literature review. *Orphanet Journal of Rare Diseases*, 12(1), 124. https://doi.org/10.1186/s13023-017-0671-8

Xie, F., Gaebel, K., Perampaladas, K., Doble, B. and Pullenayegum, E. (2014). Comparing EQ-5D valuation studies: A systematic review and methodological reporting checklist. *Medical Decision Making: An International Journal of the Society for Medical Decision Making*, 34(1), 8-20. https://doi.org/10.1177/0272989X13480852