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REVIEW

CONTEXT AND ISSUES OF SOCIAL HEALTH INSURANCE INTRODUCTION IN GEORGIA

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Abstract

The social health insurance system, unlike general tax financing system, is more focused on market mechanisms. Despite the achievements, the introduction of social health insurance in Georgia turned out to be way too difficult. Because of ongoing economic crises, the state failed to finance its promised commitments, resulting in a chronic shortage of funding for health care system. The new government abandoned the idea of building a social insurance system and switched to a general tax financing model, where the state takes a dominant lead, and the healthcare is financed from state budget. Given that the social insurance system is the best way of mobilizing additional funds and therefore providing sustainable funding for health sector, it is advisable to promote social insurance development. The healthcare sector needs consistent, continued and successive reforms. Despite the change of governments, the strategic course should not change drastically in the long run and the achievement should not be denied because of the political climate change.

Keywords: social health insurance, healthcare reforms, General Tax-financed healthcare model.

Résumé

Contexte et enjeux de l'introduction l'assurance maladie sociale en Géorgie

Le système d'assurance-maladie sociale, à la différence du système général de financement fiscal, est davantage axé sur les mécanismes de marché. Malgré les réalisations, l'introduction de l'assurance maladie sociale en Géorgie s'est avérée beaucoup trop difficile. En raison des crises économiques en cours, l'État n'a pas réussi à financer ses engagements promis, ce qui a entraîné une pénurie chronique de financement pour le système de santé. Le nouveau gouvernement a abandonné l'idée de construire un système d'assurance sociale et est passé à un modèle de financement fiscal général, où l'État prend la tête et les soins de santé sont financés par le budget de l'État. Étant donné que le système d'assurance sociale est le meilleur moyen de mobiliser des fonds supplémentaires et donc de fournir un financement durable pour le secteur de la santé, il est conseillé de promouvoir le développement de l'assurance sociale. Le secteur de la santé a besoin de réformes cohérentes, continues et successives. Malgré les changements de gouvernements, le cap stratégique ne devrait pas changer radicalement à long terme et

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la réalisation ne devrait pas être niée en raison des changements politiques.

Mots-clés: assurance-maladie sociale, réformes des soins de santé, modèle de soins de santé financé par l'impôt général.

Context of reformation

In Soviet times, Georgian health system was based on Semashko healthcare model. The model was named after Soviet doctor N.A. Semashko, who in 1918 introduced the centralized healthcare system, providing free medical care for the entire population. The Semashko healthcare system planning and administration was strictly centralized and completely excluded economic motivation for development. The healthcare facilities were all state-owned. National taxes were the source of healthcare system funding. Healthcare providers were financed on the basis of budget-items, depending on hospital capacity, number of staff and beds, resulting in inflexibility of resource management and planning[1].

Due to the strict definition of each cost item, hospitals were not allowed to redistribute resources among various types of medical services, to improve their efficiency. For increasing the funding, Medicare facilities were interested in boosting the number of staff and beds, which resulted in a reduction of quality of healthcare services. Under the existing financing system, the medical staff was not incentivized to provide high quality medical services. Due to obsolete clinical practice, the system was not adequately responsive to the needs of the population[2].

At the same time, the medical care provider (medical facility) and financing institution (Ministry of Health) were not separated from each other, i.e. the Ministry of Health was both the exclusive provider and the purchaser of medical services, correspondingly decreasing the motivation for healthcare cost monitoring and respectively, for cost containment[3].

Despite the fact that under the Soviet healthcare system, the preventive nature of medicine was declared by the state, the major effort and investments were directed to hospital services. The health system was focused on hospital sector development and less attention was paid to health promotion and prevention and the increase of the role of Primary Health Care system. Due to improperly developed primary healthcare system, the population rarely referred to it, and key medical services were provided through hospitals and specialized polyclinics. Therefore, the majority of resources was distributed on hospital section, number of bed-days spent in hospital was one of the key indicators of successful functioning of the system, which in turn, led to striving for abundance of beds and medical specialists. All the aforementioned affected the quality of medical care.

The system was more interested in artificial expansion of the network rather than meeting patients' demands and solving their problems. Despite the fact that the technological and material foundation of healthcare facilities were morally and physically obsolete or almost destroyed (more than half of healthcare facilities were built before 1940), instead of renovation of existing assets, the state allocated funds for construction of new facilities. In 1988, 115 healthcare institutions were stopped at the stage of construction, most of them being left unfinished long afterwards[4].

The higher Medical Education System, existing in Georgia, failed to meet modern international standards and today's increasing requirements. In Soviet period, the prestige of medical profession was the basic reason of medical staff abundance and relatively low qualification. The country showed the highest provision rate of physicians in the world, indicating the extensive development of healthcare system, instead of quality increase. Over 120,000 people were employed in healthcare sector[5]. In 1990, 5.2 doctors were available per 1,000 inhabitants, while this indicator in Post-Soviet Union amounted to 3.9, in EU 3.1 (in France 2.6, in Italy 2.2), and in Central and Eastern European Countries 2.4[6], in USA 2.8, and in Japan 2.1[7]. Due to low wages of healthcare workers, the incentive for high quality medical service provision was less[8].

Under the Soviet healthcare model, patients used to perceive their own health not as an economic category, towards which they should have had their own responsibility, but primarily as a concern of the socialist state. State-declared commitment "Universal and Free Medical Care" meant that the population should be provided with defined and guaranteed medical care.

Notwithstanding such guarantees, an individual's right to healthcare was to some extent enfringed, as he/she was deprived of the right of free choice of medical facility and doctor. The service was free for everyone, although the level of informal out-of-pocket

payments was high, as in most cases the patient had to pay a "doctor's remuneration" out-of-pocket.

In December 1991, after the collapse of the Soviet Union, Georgia became an independent country. With the acquired independence, over the first four years, Georgia experienced hard period of severe economic crises, emerging as a result of civil wars. Between 1990 – 1994, Gross Domestic Product per capita amounted approximately from $8,000 to $2,200, i.e., was reduced by 70%. In 1994, the annual inflation level exceeded 7840%, and industrial production was decreased by more than half[9].

The acute economic crises in the country triggered the demolition of healthcare system. State budgetary funding of medical field was also sharply reduced[10]. At the beginning of 1990s, the share of healthcare in state budget was decreased from 13.2% (1991) to 0.54%[11]. In 1985 – 1994, state healthcare expenditure per capita was decreased from $95.5 to $0.81[12]. The state share in total healthcare spending diminished to 4.9% in 1995[13]. In 1985, healthcare expenses per capita comprised 95.5 USD, in 1990 – 13 USD, and by 1994, it dropped to 0.90 USD.

The funds allocated by the state for healthcare financing were significantly lower than the minimum essential need for medical services. As a result of existing economic crisis, medical staff salaries became so symbolic that the annual incomes have been less than the monthly subsistence level.

Because of low pay, the number of nurses dropped dramatically. In Georgia, the ratio of nurses per doctor decreased from 2.2 to 1.9 in 1991-1994[14], the last place in Europe. For comparison, in the European region this ratio is 2.3 nurses per doctor, in Belgium 6, in Switzerland 5.3, and in Germany 3.4. Such a shortage of nursing staff in health sector negatively affects the quality of medical care. Due to low wages and unstable economic situation, many prominent specialists have been encouraged to quit their jobs and leave the country[15].

As a result of meager state spending on health care, people had to pay medical bills out of their own pockets. Informal out-of-pocket payments were widespread. The helpless population could not receive vital medical care because of lack of funds. Demographics of the population deteriorated: the morbidity rate had increased, the birth rate had decreased, the number of socially dangerous diseases (tuberculosis, venereal diseases) had risen[16]. The average life expectancy had decreased by 3 years and in 1995 it amounted to 70.3 years[16].

Maternal and child health has significantly deteriorated since the early 1990s. Maternal mortality increased from 20.5 to 55.1 (per 100,000 live births) between 1990 and 1995, while infant mortality scaled up from 20.7 to 28.6[17]. According to experts' estimation, 57% of infant mortality could have been avoided under better medical care management. 74.2% of stillbirths died before delivery, while 72% of patients under one year of age were hospitalized 36-48 hours late. Experts believe that only 60% of children, who died in the event of timely medical care, were hopeless. The aforementioned was related to the lack of transport and intensive neonatal care equipment, insufficient finances, nosocomial infections.

The healthcare system disruption, deterioration of sanitary-epidemiological situation and insufficient implementation of preventive measures contributed to a significant increase of infectious diseases. The situation was further complicated by non-compliance with the vaccination dates for children and adolescents, leading to the outbreak of diphtheria and other dangerous infections. The failure of the planned vaccination in 1991-1992 because of the lack of vaccines led to an epidemic of diphtheria. 23 cases of diphtheria were recorded in 1993, 312 cases in 1994, and 425 cases in 1995[18]. 42 people from the abovementioned cases have died. Cases of measles, rubella, and whooping cough have increased. Acute respiratory infections accounted for 43% of mortality in children under one year old[19]. Tuberculosis morbidity and mortality have increased dramatically, exceeding the rate in Western European countries by 90%[20]. The main reason for the spread of tuberculosis was the low level of case detection. Cases of diseases that were considered to be eliminated have increased, including malaria, visceral leishmaniasis, and rabies. Mortality due to cardiovascular disease increased by 35% because of the emergence of relatively new risk factors (socio-economic crisis, unemployment, poverty and constant stress), deteriorating quality of medical care, lack of access to medicines, high tobacco and alcohol consumption, along with unhealthy eating[21]. The number of cases of malignant tumors has also increased because of delayed doctor visits.

The difficult socio-economic situation in the country has brought the healthcare system to the brink of collapse, making it practically impossible for medical institutions to function. The state was no longer able to fulfill its duty to provide medical services to the population. Georgian medicine, in fact, found itself in a collapse.

The concept of health care reform

In searching for a solution to the acute crises of healthcare sector, an issue of applying a new model for fundamental reorganization of a self-functioning field, being on the verge of destruction, was on the agenda since the mid-1990s.

The beginning of fundamental reforms was preceded by the first public statement on reforms, made in the Parliament of Georgia on March 3, 1994. This was the parliament represented by the largest number of political entities in the history of independent Georgia, 24 parties. Despite such a diverse representative parliament, the Minister of Health was unanimously approved, thus supporting the launch of radical reforms in healthcare sector.

Similarly, the extended board held at the Ministry of Health of Georgia on October 14 of the same year, attended by the head of state of Georgia and members of the government, was very important. Based on the decision made by the board, the concept of complete reorganization of healthcare system was developed. The process of structural and qualitative reform in the health sector has been supported by the World Health Organization, the World Bank, and the governments of Japan, Germany, Sweden, and the United Kingdom.

The concept of healthcare system reorganization recognized the need of healthcare system reform, defined political, economic and legal components of the state policy strategy. The main goal of health system reorientation was to prepare and implement a healthcare organization and management model when switching to market-economic relations, which would be in line with the requirements of the country's political and economic development. The country's scarce financial resources practically excluded the comprehensive medical care, making it necessary to balance the state obligations in public health sector with its capacities. Under the new Constitution of Georgia, the state, for the first time, declared that the burden of healthcare responsibility was distributed among various entities of the state and that medical care was no longer free. The responsibility of the state was no longer comprehensive and the obligations were defined by the state healthcare programs, as well as by field (regulation) management mechanisms. The public had the right to have access to medical services provided by state health programs.

The difficult, painful and multi-stage process of healthcare system reorientation began from August 10, 1995. Healthcare reform was one of the first state reforms implemented in the recent history of Georgia, with the key goal to restore the collapsing, self-sustaining healthcare system, establishing qualitatively new relationships in the system that would be in line with the country's political and economic development requirements[22]. In 1999, the National Health Policy of Georgia and the Strategic Health Plan 2000-2009 were developed. The reform was aimed at improving equality and access to healthcare services for the population.

Introduction of health social insurance system

One of the hallmarks of health systems is funding. There are two main types of health financing: the health insurance (Bismarck) model and the general tax-funded (Beveridge) health insurance model. Under the Bismarck model, citizens are required to pay pre-determined insurance premiums to insurance funds. The insurance package covers the most needed types of medical services. The idea is that citizens are entitled to medical care by paying contributions to the insurance system. Thus, through the Bismarck model, a certain relationship is established between the contributions and the benefits received.

The national (Beveridge) model of healthcare is quite similar to the Semashko system, completely excluding the insurance principle. Instead of insurance, healthcare is completely financed from the state budget and tax revenues, in general. Under the Beveridge model, the state takes a dominant lead, compared to the Bismarck model, because healthcare organizations are more dependent on the state.

When creating a new financing system in Georgia, the choice was made in favor of social insurance model[23]. The social health insurance model implementation was conditioned by many factors:

- Introduction of market mechanisms in the country;
- Equal and equitable distribution of health responsibilities to the state, employer and employee;
- Striving for mobilizing additional funds for health sector;
- Search for sustainable funding;
- Cost containment;
- Demand for increased transparency;
- Successful Bismarck model imitation in developed European countries;
- Distrust towards strictly centralized state system and government interventions after the collapse of the Soviet Union.

The main advantage of switching to social health insurance model is related to equal and equitable distribution of responsibilities for human health between the state, the employer and the employee[24]. Here, the medical services for the insured should have been purchased by the Social Insurance Fund, instead of the state. According to the reform, the purchase and supply of medical services should be separated, which was deemed to be a mechanism of improving the medical service efficiency[25]. This relieved the state of its role as a direct provider of medical services. It had to maintain its influence over the healthcare system through strong regulatory, financial and licensing mechanisms[26].

Instead of free healthcare declared during the Soviet era, the state began to limit its healthcare obligations to its own population by creating state healthcare programs and medical standards. State health programs (at the federal and municipal levels) were put in place to provide medical care to the population within the scope of the program, which would be balanced with the economic situation of the country.

The adoption of the social health insurance (Bismarck) model in Georgia was conditioned by many factors. One of the main reasons is usually related to politics, in particular, to the political desire of distancing oneself from the Soviet system[27,28,29]. After the collapse of the Soviet Union, there were many doubts about highly centralized state system and government interventions, as in the Soviet period, funds for healthcare were allocated from the state budget on the principle of leftover funds, having remained after meeting the needs of other sectors. Therefore, the state had a political desire to finance only certain areas.

Thus, because the Beveridge model was more associated with the centralized state structures of the Soviet period (Ministry of Health), while the Bismarck model was associated with non-state, public institutions (Social Insurance Funds), preference was given to the development of the latter[30].

Also, a big role was played by the desire of sharing the Bismarck model which proved to be successful in developed European countries and especially in Germany and Austria[31,32,33]. During this time, the benefits of social insurance financing were actively discussed in the UK, where healthcare system is financed by general taxes[34].

Other factors included the search for and mobilization of additional funds for health sector and cost containment, demand for transparency increase, search for sustainable funding, and limiting policymakers 'ability to divert healthcare to other areas, creating services that meet patients' needs, and desire of introducing market-mechanisms, related to privatization of medical services[35].

The contribution of international agencies and donors to the introduction of health insurance system in Georgia is great, however, the ongoing processes in the country itself have played a crucial role. In addition, the World Health Organization and the World Bank have recommended a insurance-based health care system in many countries[36].

By choosing the social health insurance model, Georgia followed the processes ongoing in Eastern European countries. 22 out of 28 countries in the region have introduced the social health insurance system (Table 1).

In 1995, the State Health Insurance Company was established, consisting of 12 regional branches.

Table 1. Year of introduction of the health social insurance and level of contributions in Eastern Europe and former Soviet Union

Country	*Year of introduction*	*Level of contributions*
Hungary	1989	8.5%
Czech Republic	1991	13.5%
Slovakia	1991	14%
Macedonia	1991	8.6%
Estonia	1992	13%
Montenegro	1992	15%
Serbia	1992	15%
Slovenia	1992	12.92%
Croatia	1993	15%
Russia	1993	3.6%
Georgia	1995	4%
Albania	1995	3.5%
Kazakhstan	1996	3%
Kyrgyzstan	1996	2%
Poland	1997	9%
Bosnia and Herzegovina	1997	18%
Lithuania	1997	6%
Romania	1998	10.7%
Bulgaria	1999	6%
Moldova	2004	6%

The company enjoyed financial, managerial and contractual independence. According to the law, the highest advisory body of the company was Supervisory Board. Like Georgia, unified social insurance funds were established in Croatia, Hungary, Estonia, Poland, Latvia, Lithuania, Slovenia and Bulgaria[37].

The source of income for the state medical insurance company was a social health insurance contribution of 3%, of which 2% was paid by the employer and 1% by the employee. By legalizing medical "tax" and then "insurance premium", the so-called insurance risk was created. Insurance premiums were accumulated in the state health insurance company.

In addition to health insurance contributions, a central budget transfer was a source of revenue for the state health insurance company. The central budget was created by general state revenues. The central budget transfer was mainly intended for funding the state programs for those who were not employed (unemployed, part of the disabled population, the helpless, pensioners, children, IDPs).

A similar amount of social health insurance premium was introduced in Kazakhstan in 1996 – 3%, of which 2% was paid by the employer and 1% by the employee. A relatively small contribution was

imposed in Kyrgyzstan – 2%, paid entirely by employers. Also, in Russia, the employer paid in full (3.6%). In Lithuania, the social insurance contribution was 6%, paid in full by the employee. In Georgia, similar to Moldova, employers and employees equally pay for health insurance (6%). One of the highest rates of health insurance in Europe was set in Bosnia and Herzegovina – 18% (13% paid by the employee and 5% by the employer).

For the purpose of healthcare system decentralization, the burden of state funding was redistributed between central and local governments, for which local health funds were set up to receive revenues from municipal budgets. Contributions to health funds were averaged per capita, depending on the number of people living in the municipalities. The Law of Georgia "on 1997 State Budget" stipulates that local government bodies must receive at least 2.5 GEL per capita from the local budget and at least 10% of municipal budget expenditure for municipal health program funding. Municipalities had the right to increase this amount if their budget allowed. The optimal development of municipal health programs and their effective implementation greatly defined the maintenance and improvement of the country's public health.

Problems of social health insurance development

As a result of healthcare reforms, the number and scope of compulsory state health insurance programs, ie state obligations to the population in the health field, increased on a yearly basis, and spread to a wider range of the population. From February 1996 to March 1, 1997, the State Medical Insurance Company implemented only the state medical program of social assistance for the poor, with a budget of 1,400,000 GEL. Since March 1, 1997, the State Medical Insurance Company has been implementing six state medical programs (GEL 29 million). Since January 1998, the State Medical Insurance Company has been implementing 9 health insurance programs (GEL 38.8 million). By 1999, the number of insurance policy holders had increased to 700,000. Despite the achievements, the introduction of social health insurance turned out to be more difficult than expected. It was associated with a large share of the informal economy in Georgia, high unemployment and severe macroeconomic constraints. It took Georgia more than two decades to achieve a level of independence of GDP per capita. As a result, the basis for revenue increase was very small.

The healthcare system has suffered from chronic funding shortages as the state has often failed to finance its promised commitments. As a result, in 1999 the State Medical Insurance Company received only 64.2% of its approved budget[38]. The situation was similar in previous and subsequent years. Lack of public funding has a negative impact on the funding of specific health programs. In 1999, the State Medical Insurance Company received only 55.6% of the approved budget for funding the state program for dispensary supervision of the rural population, and only 23.6% for the child healthcare program[39]. The low level of funding means that policyholders under the state health insurance program will not be able to receive guaranteed medical care. For example, in 1999, the funds allocated for oncology services were sufficient for only 700 patients, while about 2100 patients were in need of these services.

Due to low state funding of healthcare system, the share of out-of-pocket direct taxes in Georgia accounted for most of the total healthcare expenditures. According to the World Bank, in 1999, only 22% of total health expenditures accounted for expenditures from state or municipal budgets or insurance funds[40].

In the initial period of the reform, the continuous deficit of state funding contributed to the spread of informal so-called "under the table" taxes, which has become a major source of income for many health care professionals[41,42]. Out-of-pocket direct payments prevent equal access to health care[43], creating negative incentives for physicians, posing a problem to system transparency, and acting as a serious obstacle to reform[44]. The high share of out-of-pocket payments by patients in total healthcare costs runs counter to health financing objectives, as access at this time depends more on the ability to pay, than on medical needs.

An effective mechanism for regulating or formalizing informal payments is the introduction of legal co-payments that can be used by physicians and hospitals for service improvement[45]. As a result of reforms introduced in 1995, taxes on certain health services that are not covered by the state program have been legalized. Tax legalization has reduced informal payments by patients. However, due to the scarcity of state funding, informal out-of-pocket payments still took place, often leading to catastrophic financial consequences for families[46].

Because of constant economic crises, the government was unable to maintain a balance between revenues and expenditures, leading to state funding reduction, accumulation of large debts towards medical organizations, and an increase of out-of-pocket private payments. Revenues from compulsory medical insurance contributions increased from GEL 21 million in 2001 to GEL 36.3 million in 2003, however, they accounted for only 5% of total health expenditures. As

a result of the budget failure in 1999, the state budget deficit was $ 150 million, and in 2003 – $ 90 million, domestic debt equaled to $ 120 million. The basic reasons behind were the faulty tax code, non-tax revenue collection failure, non-receipt of grants and loans from international donors, Georgian territories being out of control[47]. In fact, the newly formed state was unable to ensure the effectiveness of state finances and to collect taxes. The state budget share in GDP was insignificant (12% of GDP in 2004), which was one of the lowest rates in the entire post-Soviet space. Thus, the state had weak financial, economic and institutional capacity to bring about any serious changes in the economic and social fields.

The state intended to implement further reforms in the direction of social insurance. It aims to integrate financial resources, in particular by pooling the funding flows into a single "channel", ie merging health insurance contributions from central and local budgets. It involved merging municipal emergency care programs and state health insurance programs into a state health insurance company. The amalgamation of municipal and insurance programs increased the size of the population covered by insurance system, which in turn facilitated the registration of employees in the insurance fund. The more employers and employees paid health insurance premiums, the more transfers from the state budget would be reduced.

It was intended to provide a computer system for employer and employee registration, tax payment and insurance benefits. As a result, a basic package of universal medical services and a universal health insurance card would be introduced in the country. In addition to merging health funds, the reform included: a) integration of registration and reimbursement mechanisms into insurance programs to create a universal guarantee; b) stabilization of the resources required for insurance program financing; c) management of information systems and development of communication network; d) structural development, increasing the role of regional offices of the state health insurance company, in particular, in addition to supervisory functions, assigning the information management and insurance premium collection functions to them.

The key goal of the strategy for further social insurance system reformation was to reduce central budget expenditures required for public health services, to transfer the main financial burden of medical expenses to the employer and the employee, and to optimize the Georgian healthcare system. The implementation of strategic plan would allow the healthcare system to become more manageable and efficient.

After the Rose Revolution, Georgia's political leadership changed in November 2003. Reforms implemented by the new government have led to rapid and stable economic growth. Most importantly, the tax system was streamlined. There was an expectation that the tax system adjustment implemented by the new government would improve the collection of compulsory medical insurance contributions by the insurance fund. To completely overrule the previous government, the new government sacrificed initial germs of the social insurance system development in Georgia. In 2004, Georgia refused to build a social insurance system (Bismarck model) and switched to the general tax financing (Beveridge) model. The same continued in 2012, with the new political party "Georgian Dream – Democratic Georgia" coming to power. Although the new government introduced universal healthcare principles and a state program of universal healthcare entered into force, the general tax financed model (Beveridge) did not change and healthcare funding from the state budget generated by general tax revenues still continued by inertia[48].

A comparison of the reforms executed in Georgia with the healthcare system reforms implemented in Eastern European countries shows that the decision-making regarding the reforms in Georgia is mainly related to the change of governments in the country, rather than evidence-based. In many Eastern European countries, despite government changes, unlike Georgia, the social insurance system has not been replaced by a general tax system. These countries still have not given up the insurance funding principles. They remained committed to the strategic plan of healthcare reform that rejected a healthcare financing system, where the state played a more dominant role.

Conclusions

Given that the social insurance system is the best way to mobilize additional funds and therefore provide sustainable funding for the health sector, as well as to better ensure cost containment and increase the transparency of the system, it is advisable to promote the social insurance development in the country.

The case study of our country's recent past shows that the healthcare field, aimed at ensuring human health safety, needs consistent, continuous, successive, systemic approach of reforming and can not be subject to endless permanent fluctuations. The country should have long-term strategic goals and vision for healthcare system reforming, promoting efficient and consistent development of healthcare system. A wide range of stakeholders should be involved in strategy development process. A long-term policy formulation in the healthcare field is the topic and subject of

above-party consensus. Despite the change of governments, strategic course should not drastically change in the long run and the achievements should not be denied due to a change in the political situation.

Author Contributions:

T.V. conceived the original draft preparation. T.V., A.J. were responsible for conception and design of the review. T.V., A.J. were responsible for the data acquisition. T.V, A.J. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. T.V., A.J. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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