

## OVERVIEW

# The historical experience and practice of fight against tuberculosis in country which is one of the high drug resistant-tuberculosis (DR-TB) burden countries in European Union (EU)

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## Keywords

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## Summary

Despite considerable efforts and quite early initiated anti-tuberculosis (TB) actions, Lithuania still remains one of the European Union (EU) countries with the highest tuberculosis rates, especially multidrug-resistant (MDR) TB. According to the European Centre for Disease Prevention and Control, in 2016, 58 994 cases of TB were reported in 30 EU/European Economic Area (EEA) countries. MDR TB was reported for 3.7% of 36 071 cases with drug susceptibility testing results and continues to be highest in the three Baltic countries - Estonia, Latvia and Lithuania. In this article we present the Lithuanian anti-TB action history review and comparison with other countries in this area of action. Literature review was performed by using documents available

in the Martynas Mazvydas Library's resource, articles of foreign authors and archival materials.

According to archaeological studies, tuberculosis was common in Europe including Lithuania in the Middle Ages. Tuberculosis reporting started in Lithuania in 1926. The first tuberculosis sanatorium in Lithuania was opened in 1891. Patients were treated with sun bathing procedures, fresh air and sunlight. Later the treatment included pneumothorax, toracocautic, toracoplastic, treatment with gold products and other procedures. Lithuania introduced directly observed treatment, short course therapy (DOTS) in 1999, and since 2007 it has been working in accordance with the requirements of this strategy.

## The fight against tuberculosis

It is believed that mycobacterium appeared more than 150 million years ago and claimed more human lives than any other well-known pathogen [1]. Three million years ago early hominids in the East Africa might be infected with *M. tuberculosis* (MT) ancestors [2]. Presumably, approximately 35-15 thousand years ago *M. tuberculosis* complex bacteria, including *Mycobacterium africanum*, *Mycobacterium canettii*, *Mycobacterium bovis* had a common ancestor in Africa [2-4]. In Egypt tuberculosis was documented more than five thousand years ago. Skeletal abnormalities typical to tuberculosis, including Pott's deformation, were found in Egyptian mummies and clearly portrayed by the early Egyptian art [5-8]. Early humans began to migrate out of Africa more than 1.7 million years ago. These migrants were largely replaced by the subsequent wave of people over the last 35 to 89 thousand years [9]. Assumably, the migrants came with diseases, including tuberculosis. The first written documents describing TB, dating back to 3300 and 2300 years ago, were found in India and in China respectively [7, 10].

Archaeological evidence showed that tuberculosis was common in the Middle Ages in Europe. Clovis of France, who included the touch of persons with scrofula

in his coronation ceremony in 496, may have been the first European monarch to touch scrofulous persons, and for many generations his descendants claimed to have inherited his healing power. The illness was known in England and France as "king's evil", and it was widely believed that persons affected could heal after a royal touch [11, 12]. Archaeological findings proved existence of tuberculosis also in Lithuania in 14-15<sup>th</sup> and 18-19<sup>th</sup> century. In Leipalingis the excavation with spine abnormalities typical to tuberculosis was found (Fig. 1) [13]. Within the framework of the Lithuanian Mummy Project, seven spontaneously mummified human bodies from a church crypt in Vilnius, dating from the 18th-19th century, were CT-scanned to assess the presence of tuberculosis or other lung diseases. Authors encountered pulmonary lesions suggestive of cases of pulmonary tuberculosis. In addition, one case might have been affected by extra-pulmonary tuberculosis [14].

The history of tuberculosis was radically changed on 24<sup>th</sup> of March 1882 when Robert Koch gave his presentation about the etiology of tuberculosis in the Berlin Physiologists Society and declared postulates. In 1905 he was awarded the Nobel Prize for tuberculosis etiology interpretation. His Nobel lecture included a number of effective anti-TB recommendations relevant today: tuberculosis patient isolation, continued treatment in

**Fig. 1.** Human spine deformed by tuberculosis, Leipalingis, Lithuania, 14-15<sup>th</sup> century.



specialized dispensaries, information of the population, especially the patients' next of kin, their education, the need to register all TB cases because the statistical information was necessary [15, 16].

A copy of the honorary member's diploma awarded by the Vilnius (Lithuania) Medical Society to R. Koch on the 12<sup>th</sup> of December 1895 was found in the Vilnius University Library Manuscript Department Archive Fund. R. Koch's letter of thanks for this award was also stored. The Fund maintains documents attesting correspondence of R. Koch with the Vilnius Medical Society Presidents who used his findings in combating tuberculosis [17].

More vigorous action in the fight against tuberculosis was launched in Lithuania in 1911. At that time a meeting was convened in Kaunas where it was decided to establish a division of the recently created All-Russian League for Fighting Against Tuberculosis. In 1914 Association activities were terminated due to the war. In 1921, in the first Congress of Lithuanian doctors it was decided to set up Society for Combating Tuberculosis (SCT) [18]. Doctor Kazys Grinius initiated the establishment of SCT on 31 July 1924. He was elected as a Chairman and one of the editors of the publication "The fight against phthisis". SCT purpose was to combat the spread of tuberculosis. SCT disseminated information on tuberculosis, studied the causes of the disease, treatments and outcomes, founded and maintained sanatoriums, hospitals, shelters, boarding houses, children's

summer camps, tuberculosis departments in hospitals, clinics, emergency points, took care of the children's protection against tuberculosis, supported the poor patients and their families, cooperated with Lithuanian and foreign organizations. SCT in its activities followed the practice of other countries [19, 20]. In 1927 the SCT had 11 sections embracing about one thousand members. In 1934 it has expanded its activities and had 12 operating sections, 11 dispensaries, 1 sanatorium, 7 quartz lamps, 2 X-ray apparatus and 1.5 thousand members [21].

In Lithuania mortality rate from tuberculosis was counted by the City Board based on the death certificates presented by physicians. The calculations were not accurate, about 20 percent of people were buried without a death certificate. In 1926 the journal "The fight against phthisis" mentioned that the fight against tuberculosis was just beginning, while the mortality rate from tuberculosis was around 30 cases per 10000 population in Lithuania [20], in 1923 in Estonia - 25.6 cases per 10000 population, in 1925 - 22.9 cases per 10000 population [22]. In 1925 3903 people died from tuberculosis in Latvia, in 1926 - 3798 [23]. In 1920 the mortality rate from tuberculosis in Sweden reached 16.2 cases per 10000 population in the Netherlands - 14.9 cases per 10000 population, in England - 11.3 cases per 10000 population, in Denmark 10.6 cases per 10000 population [20]. In 1934 around 6 000 people died of tuberculosis in Lithuania, about 5 percent of the population had tuberculosis [18]. German and Swiss models to fight tuberculosis were considered successful. Germans maintained 17 765 beds ex gratis and nearly 3 thousand dispensaries and similar institutions [24].

In Lithuania health services were hardly available to the patients with "milder" tuberculosis (about 60 thousand). Lithuanian villages were very poor. Most of the cases remained undiagnosed. The suggested actions against tuberculosis included establishment of the outpatient departments-dispensaries, free special trainings on tuberculosis lead by doctors, school curricula about health and hygiene [20]. At the time tuberculosis was called a "disease of uneducated people", so SCT particularly focused on education: "the school must educate not only cultured but also healthy citizens" [24].

### **Tuberculin skin test (TST)**

In 1890 R. Koch presented the work about substance isolation from the tuberculosis bacteria in the tenth International Medical Conference in Berlin. R. Koch has named this substance tuberculin, it was intended to treat tuberculosis. Soon, this substance was rejected as ineffective. R. Koch injected tuberculin himself and noticed an onset of fever up to 39.6°C and unusual tremor. After this experiment R. Koch offered to use tuberculin for disease diagnostic. The Danish veterinarians continued with further tuberculin tests [25, 26]. TST is used to diagnose persons who have been sensitized by *Mycobacterium tuberculosis*, a condition referred to as latent tuberculosis infection. Clemens von Pirquet was the first

scientist who mentioned and introduced the concept of latent tuberculosis in his works. In 1907 von Pirquet created the tuberculin skin test, which was used to identify the persons who previously had been in contact with TB. It made clear that the majority of people infected with tuberculosis were asymptomatic and might suffer from active tuberculosis in the future [27]. In 1908 Charles Mantoux introduced tuberculin injections into a skin. Florence Seibert developed purified protein derivative (PPD). With an availability of well-standardized PPD, careful studies of tuberculin reaction sizes became possible and such studies led to further knowledge of mycobacterial infections. In 1952 Carroll Palmer and Leroy Batt published a large-scale research work providing assessment of tuberculin reaction in TB patients. Reaction of the five tuberculin units (PPD-S) had an average of 17 mm [28]. After three years, the World Health Organization (WHO) published a report describing reaction of the healthy school children to tuberculin, which was similar to that of patients with tuberculosis - they were diagnosed with latent tuberculosis [29].

In Lithuania 1924, 59 tuberculin tests were performed in Kaunas City Municipality Tuberculosis Dispensary. In 1934 totally 483 tests were conducted. In 1925 the Pirquet tests were performed in Kaunas city Viliampole district schools, which showed that about 80 percent of children aged 7-14 were infected with tuberculosis [22]. Tuberculin testing with Dermatubin by rubbing it into a skin was also conducted [30]. In 1938 it was decided to oblige doctors to perform tuberculin testing in all students by Dermatubin, Pirquet or Manthoux methods [31].

## Sanatorium for tuberculosis treatment

In 1859 Herman Brehmer opened the first sanatorium for tuberculosis in Germany. The rest and nutrition regimen was observed in the sanatorium. Soon sanatoriums for tuberculosis treatment were opened in other countries [32].

Effects of the sanatorium care to the disease outcome were indistinct. In 1923 G. Lissant Cox published his 5 years lasting research, the aim of which was to compare the mortality of patients treated at home and in sanatorium. The research showed that case fatality rate was higher in those (about 20 per cent.), who were treated at home [33].

In Lithuania sanatorium patients received not only a high-quality food, procedures including sunbathing (Fig. 2), ultraviolet radiation, pneumothorax (Fig. 3), irradiation with quartz lamps (Fig. 4), but toracoplasty were also applied.

First child (12 years) in the pictures is also treated for neck tuberculosis. Treatment procedure with Rollier machine is carried out by stretching his head [31].

Dr. Dakinevicius performs pneumothorax procedure in the Mazeikiai Department Dispensary [34].

Room at the Panemunes sanatorium, Lithuania [18].

Fig. 2. Sunbathing procedure in the Dr. K. Grinius sanatorium, Lithuania, 1938.



Fig. 3. Pneumothorax procedure. Mazeikiai Department Dispensary, Lithuania, 1936.



Fig. 4. Irradiation with quartz lamps, Lithuania.



In 1696 Giorgio Baglivi described improvement in condition of tuberculosis patient after experiencing traumatic pneumothorax (person was injured with a sword). The first therapeutic pneumothorax procedure was performed in London by F.H. Ramadge in 1834. In 1939 Oli Hjaltested and Kjeld To described outcomes of this procedure in 191 patients. Before the procedure, all patients were MT-positive, after procedure 65 died, 11 remained MT-positive, 8 - were treated further and 107 patients discontinued treatment because of an achieved desired result [35].

In 1891 the first sanatorium-summerhouse was built in Lithuania by military doctor Paskevicius near the Kazlu Ruda railway station. Sanatorium was assigned to individuals with "weak" lungs [22]. In 1925 the Department of Health set up sanatorium also in Jurbarkas, which had 50 beds [21]. In 1927 sanatorium was opened in Varena [34]. Similarly, the Latvian SCT maintained 3 children's sanatoriums (Ogruos, Bikernuos and Rodenpoize) with 265 beds. Also, the Latvian Red Cross (RC) had 5 sanatoriums, the Patient Fund - 6 sanatoriums (320 beds). There were several private and one public sanatoriums. Latvia had 1.100 beds in total for patients with tuberculosis. At the same time, Denmark allocated 3.5 thousand beds for patients [24]. In the special inter-war tuberculosis publication it was noted that the sanatorium had modern equipment, central heating, sewer, electric light and 17-staff personnel. Since the start of sanatorium operation until 1934 322 Lithuanians, 140 Jews, 14 German, 12 Russian and 8 Poles were treated. In 1938 a school was established at the sanatorium [22, 31]. To combat tuberculosis, SCT opened a new modern sanatorium in Alytus in 1939. Construction of the Sanatorium new building costed over 170 thousand Litas (about 50 thousand Euro). It was planned to treat 50 patients in there. One of the main objectives of SCT was to isolate incurable patients. Following the Norwegian example, SCT planned to establish colonies for incurable patients. Isolation was one of the key objectives of SCT. Colonies should be established in Alytus, Utena with capacities of each for 15 patients [21]. In 1932 a four-story brick Lithuanian RC sanatorium was established in Kaunas with designated 1.75 hectare plot of land. This sanatorium was owned by the Lithuanian RC, founded in 1919. In 1933 a private sanatorium for children owned by Prof. Dr. V. Tumeniene was established in Panemune [36].

In 1936 a possibility to employ the patients in the newly opened sanatoriums was discussed to reduce the patients' maintenance costs by recruiting patients at the sanatorium. A similar example was applied in Switzerland [34].

Sanatorium patients were treated "conservatively" and "actively". Conservative treatment was applied according to the Brehmer Dettweiler's Hygiene - Dietics system, providing the patients with the peace of mind and good quality food, fresh air and sunlight [22]. Patients were recommended to consume 2.5-3 thousand calories. The treatment included respiratory gymnastic, treatment with sunlight was administered to persons with larynx tuberculosis. Sunbath positive effect on people with tu-

berculosis was also widely discussed. Following the Berlin's good practices, it was proposed to arrange beaches at rivers in Kaunas, Panevezys and other cities [24].

Pneumothorax, neurosurgeries, oleothorax, thoracocautic, thoracoplastic procedures, filling of lung cavities, treatment with collapse have been applied in the sanatoriums. Heliotherapy, extension were used for bone and joint tuberculosis, X-ray therapy for glandular tuberculosis [22, 24]. The intercostal nerve alcoholisation treatment was also applied: alcohol used to be injected into nerves triggering the muscle paralysis [30].

In 1927 treatment of tuberculosis with gold preparation Sanokrisin were discussed. The Health Department put a ban on import of this preparation. In 1934 the treatment with gold preparations (Sanokrisin, Triphala) was applied in Panemune sanatorium [22, 24].

## Hospitals for tuberculosis treatment

Vilnius Hospital of Infectious Diseases was founded in 1905, when two brick buildings were erected for Children Infectious Diseases Hospital in Zverynas district of Vilnius. In 1911, several one store wooden buildings were additionally erected for the treatment of adult patients next to two brick buildings for the children. Patients with typhoid fever, typhus exanthematicus, epidemic relapsing fever, dysentery, cholera, meningitis, tuberculosis and trachoma were treated in this Hospital. The Hospital had 150 beds, 6 wards, 5 physicians and one microbiologist [37].

The first tuberculosis hospital was opened in Lithuania in 1923 as division of the Kaunas State Hospital. In 1926 the hospital with functionary surgery clinic was available to tuberculosis patients, patients with bone tuberculosis were referred to this Hospital. The Polyclinic-Ambulance was open every day except Sundays and holidays. X-ray costed 20 Litas (about 6 Euro), sputum examination and testing - 3 Litas (about 0.9 Euro). Poor people with permission from the City and District Board were treated for free. The National Institute of Hygiene was also accessible where research was conducted. Pulmonary patients were treated in the Kaunas Health Centre (Dispensary) where pneumothorax and sputum examination were available. It was the first health care centre in Lithuania for patients with tuberculosis. The Lung Hospital in Jurbarkas was considered one of the best hospitals in Lithuania. The Hospital maintained 50 beds, so patients had to wait in long queues. Further 80 beds were available in Varena [21].

The patients applying to the medical institutions usually suffered from neglected tuberculosis. People from rural areas often discontinued the treatment due to a lack of money [24]. The patients had to pay for the medicine themselves; some departments had agreements with pharmacies to sell medicines at lower prices. Medication for the poorest used to be reimbursed by the municipality. The patients used to receive travel, monetary and food allowances [22].



## Tuberculosis - public health problem

In 1881 doctor Herman Biggs pinpointed tuberculosis as a public health problem. In 1889 he accentuated importance of tuberculosis case reporting. In 1894 H. Biggs was able to convince the New York City Board of Health that tuberculosis must be a notifiable disease. These instructions were not required until 1897. Health care specialists opposed to these directives up to 1900 [32, 38].

Tuberculosis was attributed to the public health problems also in Lithuania. Dr. A. Domasevicius in his paper *Tuberculosis and a quest of other new ways to defeat it* in 1934 mentioned that tuberculosis was not a disease of an individual, not a family disease; tuberculosis is the disease of the general population [22].

At the beginning of the 20<sup>th</sup> century, no broader measures to combat the disease were taken in the Russian Empire. Medical Service of the Russian Ministry of Internal Affairs summoned Commission for Combating Tuberculosis, which issued a circular on measures to combat tuberculosis in 1908 and Circular on the cards for *Tuberculous disease registration* in 1909 [22]. A reporting of the tuberculosis cases started in Lithuania in 1926 [21]. A registration of tuberculosis cases and deaths was not mandatory. A consideration was given to prepare and publish a law that empowered to notify any case of open tuberculosis [24]. In the work plan/estimate for 1926, case tracing was foreseen allowing a free delivery of phlegm to the laboratory, this model was applied at the time in America. In 1933 *The law for combating contagious diseases* (CD) was passed, which enabled reporting of tuberculosis cases to the municipality, but its execution wasn't controlled [21].

## Bacillus Calmette-Guérin (BCG) vaccine

Doctor bacteriologist Albert Calmette and his colleague veterinarian Camille Guérin at the French Pasteur Institute attenuated *M. bovis* in 1921. BCG vaccine was ready for testing. A newborn, whose mother died of pulmonary tuberculosis, was first vaccinated with this vaccine. The child did not develop tuberculosis. Over the next seven years, more than 100 thousand children were vaccinated with this vaccine. The vaccine was readily available in Europe [39, 40].

In 1934 the launch of BCG vaccination was discussed in Lithuania, but this was not possible due to technical problems. One of the mentioned measures was for the National Institute of Hygiene or the Veterinary Bacteriology Institute to obtain original BCG culture from the Paris Pasteur Institute, to prepare it and supply to the hospitals and shelters through dispensaries as a preventive measure. In 1935 Kaunas was the first to start the BCG vaccination. In November, three children whose mothers had tuberculosis were vaccinated at the time of delivery. The vaccine used to be obtained from the Riga University Serological Institute [34]. It was recom-

mended to vaccinate the infants within ten days of their birth [30]. Vaccination was widely used, so in 1939 the Department of Health had planned to oblige the Dispensary Heads to perform this [22].

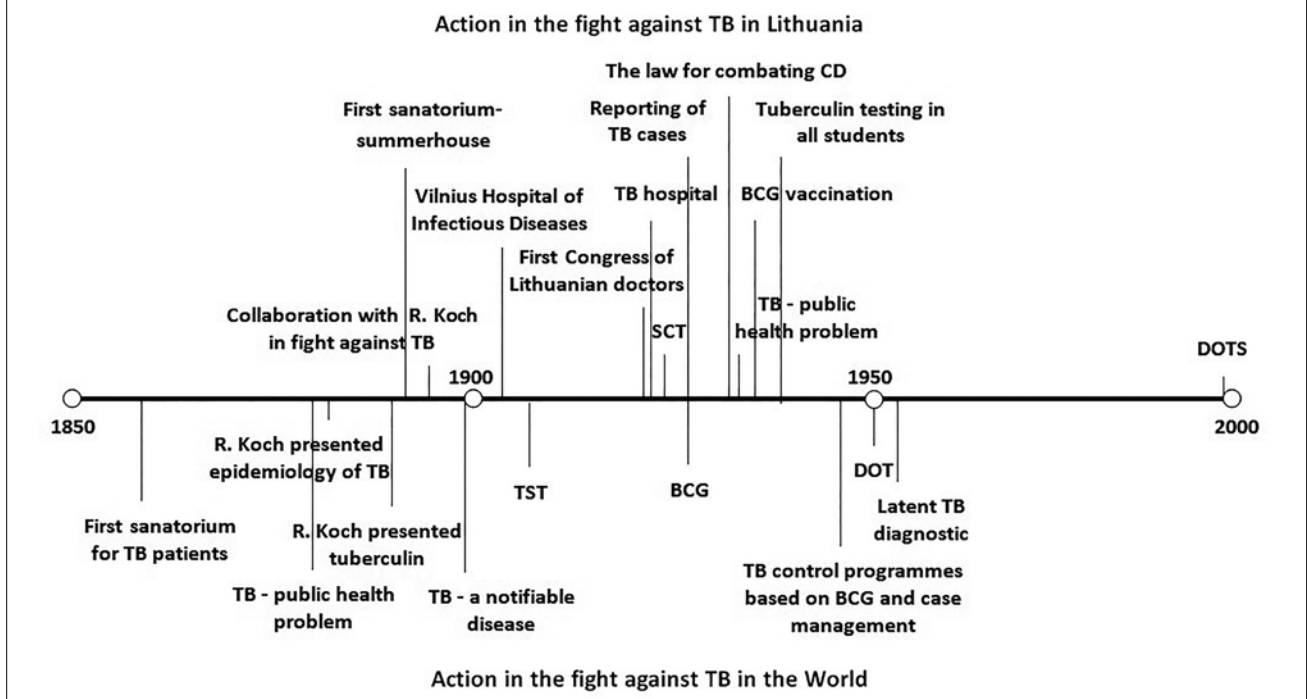
In 1947 the first WHO Expert Committee meeting took place, it was decided to assist the governments in developing effective TB control programmes based on BCG vaccination and case management. Since then, the case management has remained a major tuberculosis management strategy [41]. In 1948 United Nations International Children's Emergency Fund and the Danish RC funded campaign of tuberculin testing and BCG vaccination of those tested negative was carried out. The campaign was launched in Poland and quickly spread to other European countries. Within three years, nearly 30 million people were tested with tuberculin test, and nearly 14 million were vaccinated. This campaign was the first programme conducted by the WHO [42, 43]. In 1974 the WHO Tuberculosis Committee published the ninth report and tuberculosis control guidelines for the next two decades. The guidelines emphasized significance of the sputum microscopy and outpatient treatment calling to reach 70-80 percent vaccination coverage in the age group of less than 15-20 years [44].

In 2016 Among the Baltic States highest vaccination coverage was in Lithuania (98%), lowest in Estonia (95%) [45].

## Directly observed treatment short course

With the advent of effective chemotherapy in the mid-1950s, sanatoriums began to become superfluous. By the mid-1960s most were closed. Hospital care was no longer required to provide effective treatment. A study in Madras, in which patients with tuberculosis were randomly assigned to either sanatorium or home treatment, showed no difference in either clinical outcomes or infection in the household contacts. Sanatoriums became obsolete [46, 47]. Along with the chemotherapy, a long-term patient hospitalization became a key principle of tuberculosis control. The objective was to introduce the directly observed therapy (DOT). The first similar clinic was opened in 1950. Attempts to switch to DOT were made not only in Madras, Hong Kong [48, 49] but also in London [50, 51]. Selective DOT programmes were integrated in America in 1960. They were applied only in unreliable patients [52, 53]. DOTS was an important development in global tuberculosis policy. Increasingly, poor countries began implementing the DOTS approach; many lives were saved and many new cases averted. However, for children with tuberculosis, people with both tuberculosis and advanced disease from the human immunodeficiency virus (HIV), and the increasing proportion of patients infected with strains of tuberculosis that were already drug-resistant, the DOTS strategy provided limited options for prompt diagnosis and cure [54].

Fig. 5. Essential action in the fight against TB, 1850-2000.



Lithuania introduced DOTS in 1999 and from 2007 it has been working in accordance with the requirements of this strategy [55].

Nowadays TB is still a major public health problem, for this reason a combined strategy, based on improving drug treatment, diagnostic instruments, and prevention strategy, is necessary in order to eradicate *M. Tuberculosis* by the year 2050, as committed by the WHO [56, 57]. Despite considerable efforts (Fig. 5) Lithuania is facing a number of operational problems in a fight against TB, especially in TB case management. The mechanisms for effective follow-up of patients to prevent them from defaulting are underdeveloped [58].

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### Conflict of interest statement

None declared.

### Authors' contributions

JK and GZ performed a search of the literature and contributed to the draft of the article. JK and PK designed and conceived the review. MM and SC revised critically the article. All authors read and approved the final version of the manuscript.

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