ДИФТЕРИЯТА В ЕВРОПА, БЪЛГАРИЯ И ВАРНЕНСКА ОБЛАСТ – МИНАЛО, НАСТОЯЩЕ И БЪДЕЩЕ

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РЕЗЮМЕ
Дифтерията е остро инфекциозно заболяване, което се характеризира с тежка интоксикация, фибринозно възпаление на лигавицата на горните дихателни пътища и висок леталитет. Усложненията са чести, тежки и разнообразни – инфекциозно-токсичен шок, токсична нефропатия, дихателна недостатъчност или пневмония. В Европейския регион, дифтерията до голяма степен е под контрол благодарение на интензивната стратегия за ваксинация, но в някои страни продължава ендемичното предаване на инфекцията. Основно средство за профилактика е системното и пълно обхващане на подлежащите контингенти с противодифтерийна имунизация. В настоящото проучване разглеждаме епидемиологичните проблеми и перспективите на дифтерийната инфекция в Европейския регион и Варненска област в условията на активната имунизация с дифтериен анатоксин.

Ключови думи: дифтерия, обструкция на дихателните пътища, миокардит, ваксинопредотвратими инфекции

УВОД
Дифтерията е остро инфекциозно заболяване, което се характеризира с тежка интоксикация, фибринозно възпаление на лигавицата на горните дихателни пътища и сливиците, с тежко протичане и висок леталитет (9). Редакцията на инфекционисти (Б. Тасков, И. Диков, Ю.В. Лобзин и др) описват тежки и чести усложнения на дифтерийната инфекция като токси-инфекциозен шок (4), остър надбъбречен недостатък, миокардит, парализи на сърдечните и дихателните мускули, диафрагмата, неврити (5, 15), които в миналото и сега често водят до летален изход при заболяването от дифтерия хора.
До въвеждането на серотерапията и имунизацията с дифтериен анатоксин, дифтерията заема едно от първите места по заболеваемост и смъртност в световния план. До въвеждането на ваксината с дифтериен анатоксин била една от възможните средства за насочване на дифтерията. Съвместна с ваксината, дифтерийна антитоксинна терапия е била въведена през 1923 г. (23).

ABSTRACT
Diphtheria is an acute infectious disease, which is described as a serious poisoning, fibrinous mucosa inflammation of the upper respiratory tract, and high lethality. There are many different kinds of complications and they are severe and occur frequently - infectious toxic shock, nephrotoxicity, respiratory tract obstruction, myocarditis, polineuropathy, respiratory failure, or pneumonia. In Europe, diphtheria is largely under control thanks to the intensive vaccination strategy, but there are countries, where the endemic viral contamination still exist. The basic prevention remedy consists in the full systematic antipdiphtheritic immunization coverage of the subject quotes. In the present study, we examine the epidemiological problems and prospects of diphtheria infection in Europe and the Varna region under the conditions of active immunization with diphtheria anatoxin.

Keywords: diphtheria, respiratory tract obstruction, myocarditis, vaccine preventative infections

INTRODUCTION
Diphtheria is an acute infectious disease characterized by serious intoxication, fibrinous inflammation of the upper respiratory tract and tonsils, serious leakage and high lethality (9). Many authors - infectionists (B. Taskov, I. Dikov, U.V. Lobzin, etc.) describe many serious and frequent complications of the diphtheria infection, such as toxic infectious shock (4), acute adrenal insufficiency, myocarditis, paralysis of the heart and the respiratory muscles, the diaphragm, and neuritis (5, 15), which in the past and even now have often lead to a fatal outcome in people with diphtheria. Until the introduction of serotherapy and the immunization with diphtheria anatoxin, it was one of the world’s leading causes of morbidity and mortality. In England and Wales in 1937-1938 it ranked second after pneumonia as a cause of child mortality (32 per 100 000 deceased people in the age group under 15) (24, 26). The creation of the diphtheria anatoxin by Gaston Ramon in 1923 is an undisputed success in the fight against diphtheria (23). Its widespread use in the early 1930s and 1940s in the United States, Canada and
та. В Англия и Уелс през 1937-38 г. тя се нарежда на второ място след пневмонията като причина за детската смъртност (смъртност 32 на 100000 възрастовата група под 15 години) (24,26). Безспорен успех в борбата срещу дифтерията е създаването на дифтерийния анатоксин от Gaston Ramon през 1923 г. (23). Широкото му приложение в началото на 30-те и 40-те години в САЩ, Канада и много страни от Западна Европа, води до бързо намаляване на честотата на дифтерията в детската възраст (18).

ЦЕЛ
Да се извърши епидемиологичен анализ на достъпната епидемиологична информация относно еволюцията и съвременните аспекти на дифтерийната инфекция в България, по-специално Варненска област, Европа и света в условията на масовата активна имунопрофилактика с дифтериен анатоксин.

МАТЕРИАЛИ И МЕТОДИ
Използвани са данни и материали от национални, регионални и международни нормативни документи и приложения, касаещи дифтерийната инфекция в миналото и настоящето.

РЕЗУЛТАТИ И ОБСЪЖДАНЕ
В България заболеваемостта от дифтерия за периода от 1900 – 1961 г. при ежегодни колебания се покачва до 163,0‰ през 1936 г., и постепенно спада до 2,8‰ през 1961 г. и 0,04‰ през 1971 г. Същността от дифтерия също намалява от 13,2‰ през 1934 г. на 0,14‰ през 1961 г., както и леталитетът - от 13,5% през 1932 г. на 4,9% през 1961 г. (6, 15). Във Варненска област стойностите на дифтерийната заболеваемост и смъртност са много високи преди въвеждането на имунизацията с дифтериен токсоид (8). След въвеждането на масовата имунизация с противодифтериен ваксината дифтерията постепенно преминава в процес на елиминация, съответно през 1960 г. с 0,3‰, през 1962 г. − 0,3‰; през 1964 г. − 0,1‰; през 1965 г. − 0,6‰ и последните случаи са през 1969 г. − 0,3‰, след което клинични случаи не се регистрират. През 1990-1995 г. в някои от бившите съветски републики избухва епидемия от дифтерия, което се разпространява и в Европа. Отбелязва се рязък подем на заболеваемостта с преобладаване на дифтериата при възрастни хора. Заболяемостта в Руската федерация ежегодно е много Western European countries has led to a rapid reduction in the incidence of diphtheria in infancy (18).

AIM
The aim of this article is to carry out an epidemiological analysis of the available epidemiological information about the evolution and the contemporary aspects of the diphtheria infection in Bulgaria, more specifically in the Varna region, in Europe, and in the world, under the conditions of massive immune prophylaxis with diphtheria anatoxin.

MATERIALS AND METHODS
Data from national, regional and international regulatory documents and applications related to the diphtheria infection in the past and present, have been used.

RESULTS AND DISCUSSION
In Bulgaria, the morbidity rate of diphtheria for the period 1900-1961 rose with annual variations to 163.0% in 1936, and gradually decreased to 2.8% in 1961. and 0.04% oo in 1971. The diphtheria mortality also fell from 13.2% in 1934 to 0.14% in 1961, and the lethality changed from 13.5% in 1932 to 4.9% in 1961 (6, 15). In the Varna region, the diphtheria morbidity and mortality rates were very high before the introduction of diphtheria toxoid immunization (8). After the introduction of mass vaccination with an anti-infiltrating vaccine, diphtheria gradually entered an elimination process, the levels for 1960 were 0.3%oo, for 1962 - 0.3%oo; for 1964 - 1.1%oo; 1965 - 0.6%, and the last cases were in 1969 - 0.3%oo, after which there were no more clinical cases recorded. In the period from 1990 to 1995, in some of the ex-Soviet republics, there were breakouts of diphtheria, which spread in Europe, too. There was a sharp rise in the morbidity rate of diphtheria in adults. The incidence of the disease in the Russian Federation rose by 200% and more annually, and the mortality and lethality rates also increased. The peak of morbidity was recorded in 1994, when more than 40 000 people became sick and more than a thousand died (2). In Ukraine, for the period from 1991 to 1998, more than 19 000 people were infected, and 696 died (3). During the mass epidemic in 1995, over 50000 cases of diphtheria were registered in the European region of WHO, including 6 clinical cases in 1992 in Bulgaria (20). As a result of the dissolution of the Soviet Union, there were problems with the health services, as well as with the lack of sufficient vaccine for the prevention of the most af-
The temporary difficulties due to the transition period related to the introduction of health insurance system, in which part of the Bulgarian citizens remained un-

fected countries (7,11,16,19,26). According to WHO, in 2015 there were 4530 reported cases of diphtheria globally (21).

In the European region of WHO, as a result of the mass vaccination campaigns and the additional control measures, diphtheria morbidity has been brought under control (25), but despite all, the endemic transmission of the infection still continues in some European countries. According to ECDC data in 2014, there were 38 cases of diphtheria reported in Europe, 35 of them were confirmed by laboratory tests to have C. diphtheriae (22 cases) and C. ulcerans (13 cases) (17). Much of the patients are old people, who were unvaccinated or without any immunization data. In the last years, most cases of diphtheria in Europe have been registered in Latvia, which is defined as an endemic area (17). In Bulgaria, the compulsory immunization against diphtheria was introduced in 1951 for children under 8 years of age (13). Until 1956, doctors used the native anatoxin of G. Ramon. In this first stage of the fight against diphtheria, morbidity decreased 7 times (from 42.8% in 1952 to 6.3% in 1957) (14). In 1957, the purified, concentrated and adsorbed diphtheria anatoxin was introduced into practice, and a few years later it was included in the combined vaccines - diphtheria-tetanus (DT) and diphtheria-tetanus-pertussis.

The improved quality of the vaccine products and the organization of the immunization activities in Bulgaria led to a sharp decline in diphtheria morbidity in the country - 0.046% in 1971 (4 cases), which is 900 times lower than 1952. Primary immunization against diphtheria provides a protective level of antitoxic immunity in 94-100% of the immunized children (10).

In the immunization period a cancellation of the cyclicity of the infection still continues in some European countries. According to ECDC data in 2014, there were 38 cases of diphtheria reported in Europe, 35 of them were confirmed by laboratory tests to have C. diphtheriae (22 cases) and C. ulcerans (13 cases) (17). Much of the patients are old people, who were unvaccinated or without any immunization data. In the last years, most cases of diphtheria in Europe have been registered in Latvia, which is defined as an endemic area (17). In Bulgaria, the compulsory immunization against diphtheria was introduced in 1951 for children under 8 years of age (13). Until 1956, doctors used the native anatoxin of G. Ramon. In this first stage of the fight against diphtheria, morbidity decreased 7 times (from 42.8% in 1952 to 6.3% in 1957) (14). In 1957, the purified, concentrated and adsorbed diphtheria anatoxin was introduced into practice, and a few years later it was included in the combined vaccines - diphtheria-tetanus (DT) and diphtheria-tetanus-pertussis.

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Diphtheria in Europe, Bulgaria and Varna District - Past, Present and Future


При извършеното от нас проучване върху имунизационния обхват с ваксини срещу дифтерия, тетанус и коклюш (ДТК) установихме, че след 2000 г. обхващаемостта на подлежащите в кърмаческа възраст с 3 дози ДТК във Варненска област се движи в границите от 93,23% за 2002 г. до 96,08% за 2005г. Поради натрупан дефицит от ДТ ваксина, през 2002 г. е регистриран най-ниският относителен дял на обхващаемост при децата на 7-годишна възраст (40,96%), подлежащи на задължителна реимунизация с ДТ (Табл. 1).

Временните трудности, дължащи се на преходния период с въвеждане на здравно-осигурителната система, при която част от българските граждани остават здравно неосигурени и без избор на личен лекар, миграцията, необоснованото разширяване на противопоказанията за възрастното население и продължаващият перманентен недостиг на ваксини Тд и ТТ през 2001 г. и 2002 г., водят до «катастрофално» нисък обхват на подлежащите във всички възрастови групи - 47,35% при 11-12 годишните за 2002 г. и около 32,27% при реимунизирането с ТТ на възрастовите групи 45-55-65-75. Този индикатор е много лош сравнение със същията величина за страната през 2001 и 2002 - 66.58% и 74.38%, респективно (Табл. 2).

In 2005, the TD reimmunization rate at the ages of 12 and 17 years reached 89.80%, its rate at the active age between 25-35 years was 86.22% and 88.45% for the adult population. Although the immunization coverage level is below 90%, improving this indicator is a sign of stabilization of medical care provided by general practitioners since the start of the health reform (Table 2).

Under the conditions of elimination, the level of anti-diphtheria protective antibodies in adults diminishes due to the lack of ability to maintain the immunity with recurrent subclinical infections, which are typical for the preimmunization period (10). To stimulate the individual and collective post-immunization immunity in national immunization programs, incl. in Bulgaria (2005), regular reimmunization against diphtheria with the TD vaccine was introduced. It is given

<table>
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<tr>
<th>TD/TT</th>
<th>2001 % coverage</th>
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<tr>
<td>TD at 11-12</td>
<td>87.37</td>
<td>47.35</td>
<td>86.64</td>
<td>76.12</td>
<td>90.15</td>
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<tr>
<td>TD at 17</td>
<td>51.07</td>
<td>72.76</td>
<td>82.87</td>
<td>76.311</td>
<td>89.39</td>
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<tr>
<td>TD at 25</td>
<td>72.46</td>
<td>66.97</td>
<td>75.51</td>
<td>52.38</td>
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<td>TD at 35</td>
<td>76.85</td>
<td>74.62</td>
<td>78.85</td>
<td>53.60</td>
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<tr>
<td>TT at 45</td>
<td>28.41</td>
<td>43.80</td>
<td>67.83</td>
<td>45.54</td>
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<td>28.10</td>
<td>46.08</td>
<td>67.12</td>
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<tr>
<td>TT at 65</td>
<td>35.39</td>
<td>55.24</td>
<td>72.40</td>
<td>54.30</td>
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<tr>
<td>TT at 75+</td>
<td>42.20</td>
<td>59.17</td>
<td>68.46</td>
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<td>88.14</td>
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</table>
75г. през 2001г. и 49,56% за 2002 г. Този показател е много по - нисък в сравнение със средния имунизационен обхват с ТТ за страната през 2001 и 2002г. - 66,58% и 74,38% съответно (табл. 2). През 2005 г. реимунизацията с ТД на 12 и 17 години достига до 89,80%, при лицата в активна възраст 25-35 години - 86,22% и до 88,45% за възрастното население. Независимо от това, че нивото на имунизационен обхват е под 90%, подобряването на този показател е индикатор за стабилизиране на медицинското обслужване от общопрактикуващите лекари след старта на здравната реформа (Табл. 2).

В условията на елиминация, нивото на защитните антитела против дифтерия при възрастните намалява поради липса на възможността да се поддържа имунитета чрез повторящи се субклинични инфекции, обичайни за доимунизационния период (10). За стимулиране на индивидуалния и колективен постваксинален имунитет в националните имунизационни програми, вкл. и в България (2005 г.) бе въведена регулярна реимунизация на възрастното население против дифтерия с ваксината ТД през 10 години след 25-годишна възраст (12). През следващите години във Варненска област показателите за обхващане на подлежащите с ваксината против дифтерия се сравнили с високи, като за 2015 г. първичната имунизация с три дози комбинирана ваксина достигна до 88,75% средно 90,7% в страната и 86% в света (21). Реимунизацията против тетанус и дифтерия във всички възрастови групи се движи в границите между 81,75 % през 2015 г. до 94,97% през 2008 г. Наблюдаваният спад в имунизационното покритие на възрастното население през 2015 г. във Варненски регион се дължи на отлагане по време на медицински противопоказания (14,86% необхванати) и миграция на населението (9,49% необхванати). Това от своя страна представлява риск от внос на дифтерия от ендемични региони, които се очертават като популярни туристически дестинации и засилващата се международна миграция.

CONCLUSIONS

1. During the centuries, diphtheria has formed as a disease with an aerogenic and contact/social pathway, having high morbidity among different age groups, frequent and severe complications accompanied by high mortality and lethality.

2. High epidemiological and immunological efficiency of active immunization with diphtheria anatoxin (toxoid) is reported, sharply decreasing both diphtheria morbidity and the incidence of complications and lethal outcomes.

3. The misunderstanding of the epidemiology and prophylaxis of diphtheria resulting in a sharp decrease of diphtheria anatoxin coverage of the contingent populations led to epidemic conditions of a threatening nature and many people died in the Commonwealth of Independent States (CIS) in the 1990s.

4. Following the massive immunization campaigns and additional control measures, diphtheria in the European region of WHO has been brought under control.

5. In the past, diphtheria is a common and severe disease with high lethality in the Varna region and throughout the country. The problem was resolved after the introduction of active immunization with diphtheria anatoxin.

6. Systemic immunization with diphtheria anatoxin included in the composition of the associated bioproducts is carried out in the Republic of Bulgaria and the Varna region, overcoming the problems with the vaccine supply and the scope of the individuals, subject to immunization.
zation with diphtheria antitoxin (toxoid), the rate of infection is significantly decreased, both in terms of morbidity and mortality rates.

3. As a result of poor understanding of the epidemiology and control of diphtheria and later - a sharp reduction in the rate of infection with diphtheria antigens among the groups of population, to the epidemic situation with a threatening character and a large number of fatalities in the countries of the ODH in the 90s of the 20th century.

4. After large-scale immunization campaigns and additional measures to control, diphtheria in the European region of the WHO is under control.

5. In the past, diphtheria was a common and severe disease in the Varna region and the country as a whole. The problem was solved with the introduction of active immunization with diphtheria antitoxin.

6. In Bulgaria and the Varna region, a systematic immunization with diphtheria antitoxin, included in the vaccines, has been achieved, overcoming the problems in the provision of vaccines and coverage of the population.

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REFERENCES
4. Dikov I., Toksi-infection Donetsk, Sofia, 1989
5. Diphtheria, (methodical guidelines on clinical, diagnostic, treatment and prophylaxis in armed forces of the Russian Federation, Moscow, 1998
6. Donchev, D., K. Krysteva. Diphtheria in Bulgaria in the period of its elimination, Epidemiology, Microbiology and Infectious Diseases, 1964; 2: 40-41
8. Ivanova E., Konstantinov R. Epidemiologic characteristics, organizational-prophylactic experience on social significance of dysfunctions in Varner region and the possibility of epidemiologic control in the period of the liberation from 1878 g. to 09.IX. 1944, Akademi, 2016, XI-XII (XXX-XXXI), 2016, №1 and 2, 183-196
13. Odiseev, Xr., Vaksini i vakcinaci, Medcina
and physical culture, Sofia, 1972; 80p.

14. Polikar, A., Twenty years of specific prophylaxis of diphtheria in Bulgaria, Epidemiology, Microbiology and Infectious Diseases, 1973; 1: 58-63

15. Tasnov B., Diphtheria, Plovdiv, DI Hristo G. Danov, 1960


24. Russell WT. The epidemiology of diphtheria during the last forty years. British Medical Research Council Special Report Series 1943; 247: 1-51
