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Diphtheria: Epidemiological update and review of prevention and control strategies

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Abstract. The importance of anti-diphtheria immunity in adults through periodic booster doses of vaccine is now increasing after last years diphtheria outbreaks in Newly Independent States (NIS) and Algeria and a few cases found in Europe and USA. Diphtheria cases notified in Italy between 1991–1994 have been reported. In 1995 WHO outlined the need to review vaccination schedules against diphtheria in all countries where gaps occur in the immunity of adults. The main sero-epidemiological studies performed in adults and vaccination schedules against diphtheria in some industrialized countries have been examined. Actual situation and control strategies adopted by WHO in the NIS and implications for other countries have been briefly presented. Finally, guidelines for management, investigation and control of diphtheria have been reported, including CDCs recommendations.

Key words: Diphtheria, Epidemiology, Immunity, Vaccination

Introduction

Since the introduction of immunization against diphtheria in the 1920s there has been a remarkable reduction in the incidence of this disease: the annual numbers of reported cases in Europe declined from 16 to 0.2 per one million population from 1964 to 1983 [1, 2]. Subsequently, since the mid-1980s there has been an increase of reported cases in Eastern Europe [3]. In the 1990s diphtheria has made an important comeback in European countries. The resurgence of diphtheria has been ascribed to the outbreak in Newly Independent States (NIS) where 96% of all cases reported in Europe occurred [4, 5]. The outbreak began in 1990 in the Russian Federation and spread to Ukraine in 1991 and then in other 12 states of NIS [6].

Figure 1 shows the incidence rate of diphtheria in various NIS regions [5].

Approximately 70% of cases has been reported among persons aged 15 years or more. Case-fatality rates ranged from 2.8% in Russian Federation to 23% in Lithuania and Turkmenistan [5].

The reasons for the diphtheria epidemic are several: presence of a large number of susceptible children and adults (low immunization coverage and inappropriate primary immunization); population migrations resulting from the dissolution of the Union of Soviet Socialist Republics (USSR); lack of adequate control measures such as aggressive mass immunization in affected areas during the early phase of the epidemic [5–7]. In Algeria, a diphtheria epidemic broke out in 1993 with 163 confirmed cases and 31 deaths. 41% of the cases had been reported among subjects aged 10–19 years and 20% reported among young adults aged 20–29 years [8].

Table 1 shows the number of cases reported in the world from 1990 to 1995 [9].

At the present, because of remarkable social and political changes the free-circulation of the population keeps the risk of outbreak high in all Countries.

A progressive increase of cases was reported in Europe: from 1,778 in 1990 to 47,671 in 1994. In 1994, at least 20 imported cases of diphtheria were reported in countries in Europe, including Finland, Germany and Poland [5].

From 1991 to 1994 in Italy 4 cases of diphtheria were reported; one of them was imported from Peru. It occurred on December 1993 in a 37-years-old woman born in Peru and staying in Rome for a few days. She had severe respiratory symptoms at her arrival in Rome and she was hospitalized in a rianimatory ward. She was not treated with diphtheria antitoxin; afterwards findings on examination included a pharyngeal swab which resulted positive for toxigenic *C. diphtheriae gravis*. She died two days later and the autopsy confirmed the diagnosis of diphtheria.

The epidemic event in the former USSR and the increase of cases in Europe have proposed once again the problem of susceptibility to diphtheria of the population in the countries exposed to relevant migration and particularly in marginalized classes

Figure 1. Incidence rate of diphtheria in NIS, 1994 [5 – modified].

Table 1. Number of cases of diphtheria reported in the world (WHO, 1996) [9]

	1990		1991		1992		1993		1994		1995	
	Countries[a]	Cases	Countries[a]	Cases	Countries[a]	Cases	Countries[a]	Cases	Countries[a]	Cases	Countries[a]	Cases
AFR[c]	32	2588	23	2995	12	2869	11	2357	6	1420	16	229
AMR	41	1009	40	622	39	451	39	388	27	712	31	161
EMR	20	3604	21	1215	20	1066	20	405	20	312	19	295
EUR	31	1778	30	3209	49	5823	49	19604	49	47853	47	50466
SEAR	10	11583	11	14878	11	8795	10	8552	10	3807	7	516
WPR	32	2062	30	1844	28	1440	29	647	26	614	25	477
Total	166 (85%)[b]	22624	155 (79%)[b]	24763	159 (81%)[b]	20444	158 (81%)[b]	31953	138 (70%)[b]	54718	145 (74%)[b]	52144

[a] Number of countries reporting cases.
[b] % of all countries.
[c] Data related to Africa only show the weakness of the surveillance system in this continent.
AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific.

(homeless, alcoholics, intravenous drug users) [8, 10–12].

Sero-epidemiological studies

Immunization with diphtheria toxoid is not protective against infection by *C. diphtheriae*, but only against the toxin. Thus the same immunized persons can become asymptomatic carriers within the community [10]. However, unless there are appreciable numbers of susceptibles among the population, spread will probably be limited [13].

According to internationally accepted definitions and recent studies, the seroconversion after vaccination is considered protective if the antibody title is 0.1 IU/ml or more ('full protection'), while a title between 0.09 and 0.01 IU/ml gives an inadequate protection ('basic protection') and a title less than 0.01 IU/ml is not considered protective ('susceptibility') [14–16].

Table 2 shows the results obtained by the main sero-epidemiological studies among adults within the last years. Although the comparison of the results is limited by the different assay methods of measurements of circulating antitoxin levels used in each study [14], it is evident that a relevant proportion among the elderly has a non-protective antibody level.

Prophylaxis

Different vaccination schedules are adopted in various countries for primary immunization. In the USA are administered 3 DTP (Diphtheria-Tetanus-Pertussis) doses in the first months of life and 2 DT booster doses are administered at the 15th month and at the 4/6th year of age [25, 26]. The vaccination schedule includes a Td (Tetanus-diphtheria for adult use) dose at 14/16 years of age [27].

In Western Europe, vaccination schedules are not homogeneous but almost all countries complete the primary immunization by the first year of age. In East European Countries vaccination against diphtheria is compulsory and provides 3 or 4 doses in the first months of life and not less than 2 booster doses in the following years [28–30]. Table 3 shows the different prophylaxis schedules adopted in Europe.

In Italy, the vaccination schedules, according to the law, provide the administration of 3 primary doses of DT vaccine from the 3rd month of life, after 6–8 weeks, between the 10th and 11th month and a booster dose before the admission to primary school [29, 31]. In 1982 a new scheme including booster doses only for tetanus every 10 years was recommended [31]. Subsequently, in 1993, the Italian Ministry of Health also elaborated a series of recommendations regarding the control of infectious and diffusive diseases in relation to the last considerable migration flow. In particular, some guidelines have been suggested for the obligatory vaccinations in under-age immigrants. They recommend that, in children of school age, the antibody title against

Table 2. Main sero-epidemiological studies performed in > 18 years old subjects to evaluate immunity against *C. diphtheriae*

Authors	Year	Geographic area	Sample age	Number of subjects	Antibody title: < 0.01 IU/ml	Antibody title: 0.01–0.09 IU/ml	Antibody title: ≥ 0.1 IU/ml
Crossley et al. [17]	1979	USA	18–39	74	62.2%	–	–
			40–59	51	90.2%	–	–
			≥ 60	58	84.5%	–	–
Weiss et al. [18]	1983	USA	≥ 50	239	51.5%	–	–
			≥ 65	109	44.1%	–	–
Galazka et al. [19]	1989	Poland	20–29	150	–	–	49%
			30–39	96	–	–	51%
			40–49	98	–	–	36%
			50–59	106	–	–	41%
			60–90	44	–	–	55%
Cellesi et al. [20]	1989	Italy	20–29	114	14.9%	–	–
			30–39	129	25.6%	–	–
			40–49	120	36.7%	–	–
			50–59	108	38.9%	–	–
			60–69	92	23.9%	–	–
			≥ 70	80	17.5%	–	–
Maple et al. [16]	1995	UK	20–29	250	25.2%	34.4%	40.4%
			30–39	250	37.2%	34.0%	28.8%
			40–49	250	35.2%	30.8%	34.0%
			50–59	250	52.8%	26.8%	20.4%
WHO [21]	1995	Poland	19–24	51	–	–	78.4%
			25–49	26	–	–	73.1%
			50–65	14	–	–	64.3%
WHO [22]	1995	France	40–64	275	–	–	46%
			≥ 65	412	–	–	33%
Comodo et al. [23]	1996	Italy	20–29	88	10.2%	58.0%	31.8%
			30–39	81	24.7%	46.9%	28.4%
			40–49	83	37.3%	55.4%	7.2%
			50–59	85	50.6%	42.4%	7.1%
			60–69	90	51.1%	38.9%	10.0%
			≥ 70	93	46.2%	51.6%	2.2%
Bergamini et al. [24]	1996	Italy	21–40	86	19.8%	–	–
			41–60	90	40.0%	–	–
			≥ 60	99	51.5%	–	–

Table 3. Legal status and schedules of vaccination against diphtheria in the European Union [28–30]

Country	Compulsory	Primary immunization			Booster doses					
Austria	No	3	4	5	16–18	–	7	14–15	–	–
Belgium	No	3	4	5	13	–	6	–	–	–
Denmark	No	5	6	15	–	–	–	–	–	–
Finland	No	3	4	5	20–24	–	11–13	–	–	–
France	Yes	2	3	4	18	–	6	11	15	18
Germany	No	3	4	5	24	–	6	11–15	–	–
Greece	No	2	4	6	18	4	14–16	–	–	–
Ireland	No	2	3	4	–	–	5	–	–	–
Italy	Yes	3	5	10–11	–	–	5–6	–	–	–
Luxembourg	No	2	3	4	18	–	5	15	–	–
Netherlands	No	3	5	7	11	–	4	9	–	–
Portugal	Yes	2	4	6	18	5	–	–	–	–
Spain	No	3	5	7	18[a]	–	–	–	–	–
Sweden	No	3	5	12	–	–	10	–	–	–
United Kingdom	No	2	3	4	–	–	4	–	–	–
		months of age				years of age				

[a] In a few autonomous communities.

tetanus must be determined, and considered as an indicator of a previous antidiphtherial immunization. Therefore, non-immunized subjects will be submitted to DT or Td vaccinations, according to the vaccinal schedules in use [32]. The last guidelines, published on 1994, recommend the administration of diphtheria-tetanus vaccine, instead of tetanus vaccine alone, in case of trauma or wound and outline the importance of a booster dose in pre-school age and the administration of a diphtheria vaccination or a booster dose in case of a journey in epidemic areas [30]. Recently, Italian Interdisciplinary Study Group on Vaccinations have proposed a new schedule providing Td booster doses every 10 years, after the first 4 doses [33].

The actual immunization policy in most Western European Countries, not compulsory everywhere, provides the primary immunization with three doses below 1 year of age, as suggested by WHO, but not a systematical administration of a booster dose in adults. In these countries diphtheria cases are rare and the number of carriers is low: thus, the opportunity for acquiring or reinforcing natural immunity is reduced. The large presence of susceptible persons constitutes an epidemic potential [8]. As a consequence, WHO recommends in all countries besides the achievement of at least 90% coverage below one year of age, also the maintenance of immunity levels by administering booster doses. In addition to the DTP and DT vaccines at pre-school and school age, Td boosters should be administered every 10 years [8].

Coverage with booster doses in older children, adolescents and young adults is feasible in primary schools, secondary schools, summer camps and military service. In contrast, lifelong immunization of adults presents operational problems. It is possible to solve such difficulties adopting two strategies: replacing monovalent tetanus toxoid for injured persons with Td vaccine and immunizing high risk

Table 4. Summary guide to tetanus prophylaxis in routine wound management (CDCs 1991) [35]

History of adsorbed tetanus toxoid (doses)	Clean, minor wounds		All other wounds[a]	
	Td[b]	TIG	Td[b]	TIG
Unknown or < three	Yes	No	Yes	Yes
⩾ three[c]	No[d]	No	No[e]	No

[a] Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.

[b] For children < 7 years old; DTP (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ⩾ 7 years of age, Td is preferred to tetanus toxoid alone.

[c] If only three doses of *fluid* toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.

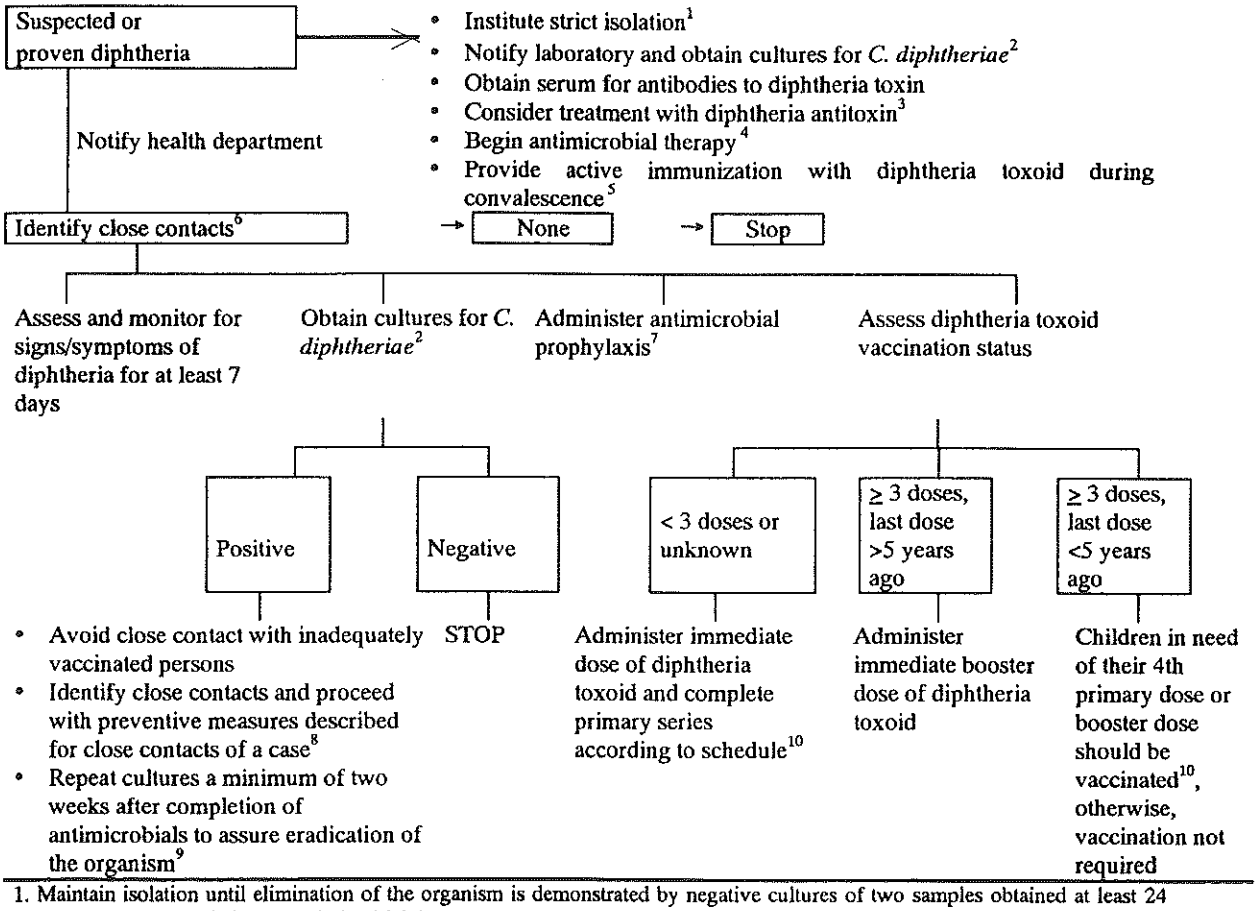
[d] Yes, if > 10 years since last dose.

[e] Yes, if > 5 years since last dose (more frequent boosters are not needed and can accentuate side effects).

groups likely to be exposed to diphtheria infection (health service personnel, military personnel, teachers, travelers, patients in long-term care facilities) [8, 34].

CDCs recommend to use Td vaccine for adults in case of trauma or injury, as reported in Table 4 [35]. The Italian Ministry of Health adopts the same scheme but recommends, in case of 'multiple and/or highly suspicious wounds' the administration of tetanus immunoglobulins even if the subject has already received 3 or more doses of adsorbed tetanus toxoid in the past [30, 31].

The vaccines are constituted by purified and adsorbed anatoxins. The doses used for primary immunization in children up to 7–8 years are 10–25 Lf units (Limes flocculation units) for diphtherial anatoxin and 10 Lf units for tetanic toxin; in adults a reduced dose of diphtherial anatoxin is prescribed.



1. Maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antimicrobial therapy.
2. Both nasal and pharyngeal swabs should be obtained for culture.
3. Before the administration of equine diphtheria antitoxin, patients should be tested for sensitivity to horse serum and, if necessary, desensitized. The recommended dosage and route of administration depend on the extent and duration of disease.
4. Antimicrobial therapy is not a substitute for antitoxin treatment. Intramuscular procaine penicillin G (25000 to 50000 units/[kg × d] for children and 1.2 million units/d for adults, in two divided doses) or parenteral erythromycin (40 –50 mg/[kg × d], with a maximum of 2 g/d) has been recommended until the patient can swallow comfortably, at which point oral erythromycin in four divided doses or oral penicillin V (125–250 mg four times daily) may be substituted for a recommended total treatment period of 14 days.
5. Vaccination is required because clinical diphtheria does not necessarily confer immunity.
6. Close contacts include household members and other persons with a history of direct contact with a case-patient (e.g., caretakers, relatives, or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case-patient.
7. A single dose of intramuscular benzathine penicillin G (600000 units for persons <6 years of age and 1.2 million units for persons ≥6 years of age) or a 7-to 10-day course of oral erythromycin (40 mg/[kg × d] for children and 1 g/d for adults) has been recommended.
8. Preventive measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of a case.
9. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and should submit samples for follow-up cultures.
10. Refer to published recommendations for the schedule for routine administration of DTP.

Figure 2. Respiratory diphtheria – recommendations for case management and investigation of close contacts (CDCs 1993) [39 – modified].

The association between the tetanic and diphtherial toxoids causes a modest increase in costs for the National Health System and the possibility of an increase of side effects such as pain, swelling, tenderness, erythema, slight increase of body temperature, weakness. Such reactions are ascribable to the adjuvant (phosphate or aluminium hydroxide) included in the vaccine and are much more common in subjects older than 18 years. Severe reactions can be excluded due to the low dosage of diphtheria toxin in the preparation vaccine for adults (< 2 Lf units) [15, 21, 36–38].

In 1993 CDCs also elaborated a plan-chart for case management and investigation of close contacts for respiratory diphtheria cases (Figure 2) [39]. The following literature substantially confirms all that suggested [25, 40]. Benenson also recommends that all close contacts of a suspected or proven case be taken away from jobs involving handling of foods (especially milk) or assistance to not immunized children during the period of their surveillance and the objects used and contamined by patient's secretions be disinfected.

Italian updating guidelines outline the importance of measures of antimicrobial and vaccinal prophylaxis and of health survey for household members and close contacts of a diphtheria case [30].

Update on diphtheria epidemic in the NIS and review of control strategies

Recently, WHO has diffused that overall reported diphtheria cases in the NIS in 1995 increased by 5.8% compared to 1994. However, by the end of the some year, most countries began reporting decreases in comparison with the same period in 1994. Moreover, in the first quarter of 1996, reported diphtheria cases in the NIS decreased by 59% to 6,179 from 14,931 cases reported in the same period of 1995 [41]. Figure 3 shows the percentage change in number of diphtheria cases reported in the NIS in this period. All countries except Turkmenistan reported fewer cases. These data represent the results of WHO control strategies against diphtheria epidemic adopted by governmental and nongovernmental organizations from 1995: (a) achievement of very high levels of routine childhood coverage (over 95%) and very high vaccination coverage among adults and children (over 90%) with a single age-appropriate dose; (b) improvement of early diagnosis and treatment of cases; (c) correct management of close contacts of cases [42]. Moreover, WHO suggests that additional doses of diphtheria toxoid for at least certain portions of the population (such as adults 30–40 years of age) will be needed to fully protect all individuals [41]. In countries which have achieved high adult coverage, incidence rates have fallen. In Turkmenistan, immunization campaigns aimed at children were carried out in 1995; adults are being targeted in 1996. Azerbaijan, Republic of Moldova, Russian Federation, and Tajikistan have successfully implemented the vaccination coverage among the entire adult population. The first two mentioned countries and Lithuania have also adopted WHO recommendation to use empirical antibiotic treatment for close contacts of diphtheria cases.

Finally, ongoing surveillance to track the course

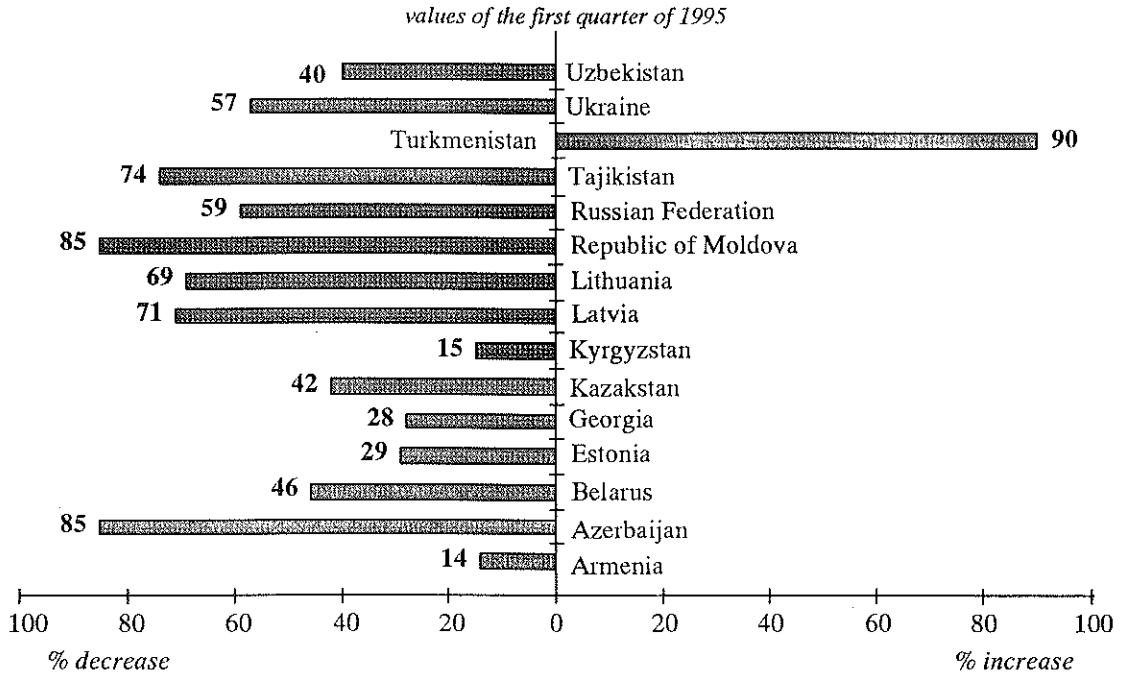


Figure 3. Percentage change in number of diphtheria cases in the NIS between the first quarter of 1995 and the same period of 1996 (WHO 1996) [41].

of the epidemic in each country and additional field studies are needed. In spite of international efforts and improvements up to now obtained, WHO still considers the epidemic to be an international public health emergency and funds for some countries in the NIS continue to lack [41, 42].

The diphtheria epidemic in Eastern Europe presents a series of implications for other countries where disease is controlled since several decades: (a) travellers going to the epidemic/endemic areas should have completed the primary immunization and have received the last dose of vaccine (primary or booster dose) within the previous 10 years; (b) diphtheria cases must be promptly recognised and diagnosed; (c) vaccination policies must have the goal of maintaining an adequate immunization coverage in all population [42].

Conclusions

The last epidemic events and world-wide increase of diphtheria morbidity show the need of maintaining high immunization coverage in all ages in population and of accessible and reliable laboratory screening, particularly for detection of toxigenic strains [43]. In 1985 some Canadian epidemiologists suggested the uselessness of administering booster doses against diphtheria and tetanus and recommended to concentrate efforts and resources only on primary immunization programmes [44]. They based their considerations on analysis of morbidity and mortality trends for diphtheria and tetanus in their country. However, the recent diphtheria outbreaks show that strategies in the prevention of infectious diseases cannot be based on national epidemiological analysis but they must consider the different health conditions outside the territorial borders and the continuous social and political changes involving all the countries in the world.

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