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# 5 Diphtheria

## Key information

Mode of transmission	Contact with respiratory droplets or infected skin of a case or carrier or, more rarely, contaminated articles.
Incubation period	Usually 2–5 days, occasionally longer.
Period of communicability	Variable; usually 2 weeks or less, seldom more than 4 weeks. Carriers may shed for longer. Effective antimicrobial therapy promptly terminates shedding.
Funded vaccines	DTaP-IPV-HepB/Hib (Infanrix-hexa). DTaP-IPV (Infanrix-IPV). Tdap (Boostrix). Td (ADT Booster).
Dose, presentation, route	0.5 mL per dose. DTaP-IPV-HepB/Hib: pre-filled syringe and glass vial. The vaccine must be reconstituted prior to injection. DTaP-IPV, Tdap, Td: pre-filled syringe. Intramuscular injection.
Funded vaccine indications and schedule	6 weeks, 3 months and 5 months: DTaP-IPV-HepB/Hib. 4 years: DTaP-IPV. 11 years: Tdap. 45 and 65 years: Td (administration not funded). During pregnancy (from 16 weeks' gestation): Tdap. For (re-)vaccination of eligible patients: DTaP-IPV-HepB/Hib, DTaP-IPV, Tdap or Td. For testing for primary immune deficiencies: Td.
Dose interval between Td and Tdap	No minimum interval is required between Td and Tdap, unless Tdap is being given as part of a primary immunisation course.
Vaccine efficacy/effectiveness	87–98 percent protection has been demonstrated using population-based analysis. Immunised cases have been shown to have less severe disease.
Herd immunity	≥70 percent of the childhood population must be immune to diphtheria to prevent major community outbreaks.

## 5.1 Bacteriology

Diphtheria is a serious, often fatal, toxin-mediated disease caused by *Corynebacterium diphtheriae*, a non-sporulating, non-encapsulated, gram-positive bacillus. Rarely, it may also be caused by other toxin-carrying *Corynebacteria* species, such as *Corynebacterium ulcerans*.

## 5.2 Clinical features

Classic diphtheria characteristically involves membranous inflammation of the upper respiratory tract, with involvement of other tissues, especially the myocardium and peripheral nerves. The organism itself is rarely invasive, but a potent exotoxin produced by some strains (toxigenic strains) causes tissue damage through local and systemic actions. There is also a cutaneous form of diphtheria, which is typically less severe. The detection of either *C. diphtheriae* or *C. ulcerans* is notifiable to the medical officer of health, and the isolates should be referred to the Institute of Environmental Science and Research (ESR) for toxin detection. Transmission is by respiratory tract droplets, or by direct contact with skin lesions or contaminated articles. Cutaneous toxigenic diphtheria is more efficiently transmitted than respiratory toxigenic diphtheria.<sup>1, 2</sup> Humans are the only known host for diphtheria, and the disease is usually spread by close personal contact with a case or carrier, or occasionally by fomites or food. The disease remains communicable for up to four weeks after infection, but carriers of *C. diphtheriae* may continue to shed the organism and be a source of infection for much longer.

Diphtheria has a gradual onset after an incubation period of two to five days. Symptoms and signs may be mild at first, but progress over one to two days with the development of a mildly painful tonsillitis or pharyngitis with an associated greyish membrane. Diphtheria should be suspected particularly if the membrane extends to the uvula and soft palate. The nasopharynx may also be obstructed by a greyish membrane, which leaves a bleeding area if disturbed. The breath of a patient with diphtheria has a characteristic mousy smell.

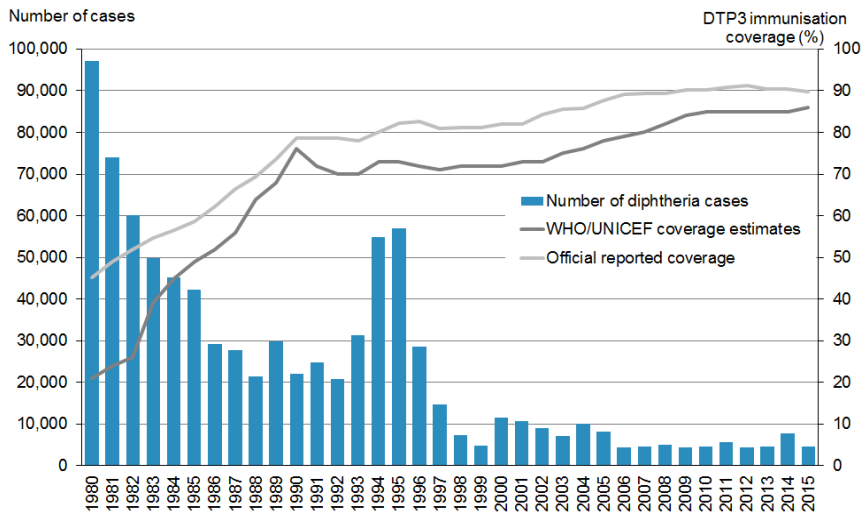
The major complication of diphtheria is respiratory obstruction, although the majority of deaths are due to the effects of diphtheria toxin on various organs. Of particular importance are the effects of the toxin on the myocardium (leading to myocarditis and heart failure), peripheral nerves (resulting in demyelination and paralysis), and the kidneys (resulting in tubular necrosis). The neuropathy begins two to eight weeks after disease onset, while the myocarditis can be early or late.

## **5.3 Epidemiology**

### **5.3.1 Global burden of disease**

In the pre-immunisation era diphtheria was predominantly a disease of children aged under 15 years; most adults acquired immunity without experiencing clinical diphtheria. Asymptomatic carriage was common (3–5 percent) and important in perpetuating both endemic and epidemic diphtheria. The global incidence of diphtheria dropped dramatically during the 20th century. Immunisation played a large part, but may not be wholly responsible for this reduction (see Figure 5.1). The estimated total number of diphtheria cases globally has fallen from just under 100,000 cases in 1980 to 4,530 cases in 2015.<sup>3</sup> Approximately half of the diphtheria cases in 2015 occurred in India.<sup>4</sup>

**Figure 5.1: Diphtheria global annual reported cases and DTP3\* immunisation coverage, 1980–2015**



\* DTP3 refers to the third dose of diphtheria, tetanus and pertussis vaccine.

Source: World Health Organization. *Immunization, Vaccines and Biologicals: Monitoring and surveillance – Data, statistics and graphs*. URL:

[http://www.who.int/immunization/monitoring\\_surveillance/data/en/](http://www.who.int/immunization/monitoring_surveillance/data/en/) (accessed 13 February 2017).

Immunisation leads to the disappearance of toxigenic strains, but a bacteriophage containing the diphtheria toxin gene can infect and rapidly confer toxigenicity to non-toxigenic strains. This makes the return of epidemic diphtheria a real threat when there is insufficient herd immunity, as happened in the states of the former Soviet Union during 1990–97. Factors contributing to this epidemic included a large population of susceptible adults, decreased childhood immunisation, suboptimal socioeconomic conditions and high population movement.<sup>5</sup> Diphtheria remains endemic in these countries, as well as in countries in Asia and the South Pacific, including Afghanistan, Bangladesh, Cambodia, China, India, Indonesia, Malaysia, Nepal, Pakistan, Papua New Guinea, the Philippines, Thailand, Vietnam and the Pacific Islands.<sup>6,7</sup>

Diphtheria is rare in high-income countries such as New Zealand due to active immunisation with diphtheria toxoid-containing vaccine.

However, continuing endemic cutaneous diphtheria in indigenous communities has been reported from the US, Canada and Australia. Small diphtheria outbreaks still occur in high-income countries.<sup>8</sup> These often appear to be caused by unvaccinated or partially vaccinated individuals travelling to endemic countries.

The overall case fatality rate for clinical diphtheria is 5–10 percent, with higher death rates (up to 20 percent) among persons younger than 5 and older than age 40 years. The case-fatality rate for diphtheria has changed very little during the last 50 years.<sup>9</sup>

### **5.3.2 New Zealand epidemiology**

Diphtheria infection was common in New Zealand until the 1960s. The last case of toxigenic respiratory diphtheria was reported in 1998.<sup>10</sup> Low numbers of cutaneous toxigenic diphtheria are regularly notified in New Zealand: two confirmed cases were notified in 2015 in refugees from Afghanistan, and two cases were notified in 2014.<sup>11</sup> These cases required large-scale public health responses to identify, prophylax and vaccinate local contacts.<sup>7</sup>

Travel to endemic countries is an important risk factor for infection, but transmission within New Zealand can occur to susceptible contacts of cutaneous cases. Tattooing practices in the Pacific Islands have also been implicated in outbreaks in New Zealand.<sup>12</sup>

The 2005–2007 National Serosurvey of Vaccine Preventable Diseases found that 61 percent of 6–10-year-olds, 77 percent of 11–15-year-olds, 71 percent of 16–24-year-olds, 48 percent of 25–44-year-olds and 46 percent of ≥45-year-olds had presumed protective levels of diphtheria antibody.<sup>13</sup> The decline apparent with age suggests there is likely to be a large and increasing pool of adults who may be susceptible to diphtheria in New Zealand, despite the introduction of adult tetanus and diphtheria (Td) vaccination in 1994.

## 5.4 Vaccines

Diphtheria toxoid is prepared from cell-free purified diphtheria toxin treated with formaldehyde. It is a relatively poor immunogen, which, to improve its efficacy, is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide.

Diphtheria toxoid is only available as a component of combination vaccines (in New Zealand as DTaP-IPV-HepB/Hib, DTaP-IPV, Tdap and Td).

See Appendix 1 for the history of diphtheria toxoid-containing vaccines in New Zealand.

### 5.4.1 Available vaccines

#### Funded diphtheria vaccines

The diphtheria toxoid-containing vaccines funded as part of the Schedule are as follows.

DTaP-IPV-HepB/Hib (Infanrix-hexa, GSK): diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B and *Haemophilus influenzae* type b vaccine, which contains:

- not less than 30 IU of diphtheria and 40 IU of tetanus toxoids and three purified *Bordetella pertussis* antigens (25 µg of pertussis toxoid; 25 µg of filamentous hemagglutinin; 8 µg of pertactin, a 69 kilodalton outer membrane protein) adsorbed onto aluminium salts
- three types of inactivated polio viruses: 40 D-antigen units of type 1 (Mahoney), 8 D-antigen units of type 2 (MEF-1) and 32 D-antigen units of type 3 (Saukett)
- 10 µg of purified major surface antigen (HBsAg) of the hepatitis B virus (HBV)
- 10 µg of purified polyribosylribitol phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type b (Hib), covalently bound to 20–40 µg tetanus toxoid, adsorbed onto aluminium salts

- lactose, sodium chloride, Medium 199, potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate and polymyxin B sulphate, which are also present as other components or as trace residuals from the manufacturing process.

DTaP-IPV (Infanrix-IPV, GSK): diphtheria, tetanus, acellular pertussis and inactivated polio vaccine, in the same quantities as for Infanrix-hexa above. Other components and residuals include sodium chloride, aluminium salts, Medium 199, potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 80, glycine, formaldehyde, neomycin sulphate and polymyxin B sulphate.

Tdap (Boostrix, GSK): a smaller adult dose of diphtheria toxoid and pertussis antigens together with tetanus toxoid. Tdap contains not less than 2 IU of diphtheria toxoid, not less than 20 IU of tetanus toxoid, 8 µg of pertussis toxoid, 8 µg of filamentous hemagglutinin and 2.5 µg of pertactin, adsorbed onto aluminium salts. Other components and trace residuals include sodium chloride, formaldehyde, polysorbate 80 and glycine.

Td (ADT Booster, Seqirus (NZ) Ltd): a smaller adult dose of diphtheria toxoid together with tetanus toxoid. Td contains not less than 2 IU of purified diphtheria toxoid and not less than 20 IU of purified tetanus toxoid. Other components and residuals include aluminium hydroxide, sodium chloride, sodium hydroxide and formaldehyde.

## Other vaccines

Other diphtheria toxoid-containing vaccines registered (approved for use) and available (marketed) in New Zealand are:

- Tdap: Adacel (Sanofi)
- Tdap-IPV: Adacel Polio (Sanofi).

### 5.4.2 Efficacy and effectiveness

Immunity against diphtheria occurs via an antibody-mediated response to the diphtheria toxin and is primarily of the IgG type. Antitoxin antibodies can pass through the placenta to provide passive immunity to the newborn.

Although there are no randomised controlled studies on the efficacy of the vaccine, between 87 and 98 percent protection has been demonstrated using population-based analyses. Immunised cases have been shown to have less severe disease, as highlighted during the outbreak in the former Soviet Union.

Vaccines combining pertussis antigens with diphtheria and tetanus toxoids have been gradually introduced into immunisation schedules throughout the world. Immunogenicity data for these combination vaccines is discussed in section 14.4.2.

## **Herd immunity**

Although immunisation is more effective at preventing disease than preventing infection, it does create herd immunity via reducing carriage and therefore transmission.<sup>14</sup> To prevent major community outbreaks, it has been suggested that 70 percent or more of the childhood population must be immune to diphtheria.<sup>15, 16</sup> This may explain the control of diphtheria in New Zealand despite historically relatively poor coverage.

## **Duration of immunity**

Diphtheria antitoxin levels decline over time in children after they have received a primary series of vaccines and a booster dose is required. In countries where diphtheria immunisation is common practice and high coverage rates are achieved, there will be no natural boosting from circulating disease, and antitoxin levels declining with increasing age may result in a susceptible adult population.<sup>17</sup>

Despite this, there has been minimal disease in high-income countries, suggesting that antibody levels may not be a reliable guide to protection and that other factors may be operating.<sup>18</sup> For example, a high proportion of the adult German population have low antibody levels, indicating susceptibility, yet this has not led to diphtheria outbreaks despite Germany's relative geographical proximity to the former Soviet Union.<sup>19</sup>

The duration of protection after Tdap boosters is unknown, but the results of an Australian study have shown that five years after the Tdap booster dose, 94.4 percent of adults had seroprotective levels of antibodies against diphtheria, compared with 93.7 percent who received Td vaccine.<sup>20</sup>



### 5.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*.<sup>21</sup> Store at +2°C to +8°C. Do not freeze.

DTaP-IPV-HepB/Hib and Td should be stored in the dark.

DTaP-IPV-HepB/Hib (Infanrix-hexa) must be reconstituted by adding the entire contents of the supplied container of the DTaP-IPV-HepB vaccine to the vial containing the Hib pellet. After adding the vaccine to the pellet, the mixture should be shaken until the pellet is completely dissolved. Use the reconstituted vaccine as soon as possible. If storage is necessary, the reconstituted vaccine may be kept for up to eight hours at 21°C.

### 5.4.4 Dosage and administration

The dose of DTaP-IPV-HepB/Hib, DTaP-IPV, Tdap or Td vaccine is 0.5 mL, administered by intramuscular injection (see section 2.2.3).

#### Co-administration with other vaccines

DTaP-IPV-HepB/Hib, DTaP-IPV, Tdap or Td vaccine can be administered simultaneously (at separate sites) with other vaccines or IGs.

## 5.5 Recommended immunisation schedule

**Table 5.1: Immunisation schedule for diphtheria-containing vaccines (excluding catch-up)**

Age	Vaccine	Comment
6 weeks	DTaP-IPV-HepB/Hib	Primary series
3 months	DTaP-IPV-HepB/Hib	Primary series
5 months	DTaP-IPV-HepB/Hib	Primary series
4 years	DTaP-IPV	Booster
11 years	Tdap	Booster

45 years	Td <sup>a</sup>	Booster
65 years	Td <sup>a</sup>	Booster
Pregnant women (recommended to be given from 16 weeks' gestation of every pregnancy, preferably in the second trimester, but at least two weeks before birth; funded when given any time in second or third trimester)	Tdap	Booster <sup>b</sup>

a The Td vaccine is funded at ages 45 and 65 years, but not the administration.

b The Tdap booster during pregnancy is for protection against pertussis (see section 4.1.2).

### 5.5.1 Usual childhood schedule

A primary course of diphtheria vaccine is given as DTaP-IPV-HepB/Hib (Infanrix-hexa) at ages 6 weeks, 3 months and 5 months, followed by a dose of DTaP-IPV (Infanrix-IPV) at age 4 years (Table 5.1). A booster is given at age 11 years (school year 7), which includes a pertussis component given as the vaccine Tdap (Boostrix).

If a course of immunisation is late or interrupted for any reason, it may be resumed without repeating prior doses (see Appendix 2).

### Alternatives to pertussis-containing vaccines

Some parents or guardians may ask about alternatives to pertussis-containing vaccines. The recommended and funded vaccines for children are those described above. There are no diphtheria-only or tetanus-only vaccines available. The Td vaccine contains half the amount of tetanus toxoid and one-fifteenth the amount of diphtheria toxoid compared to the DTaP-containing vaccines. Td was not clinically designed or tested for use to provide the primary vaccine course in children and it is not registered for use in children aged under 5 years. Although there are no safety concerns relating to administration of the vaccine, there is no data on the use of this vaccine for a primary course in children and it is not recommended.

## **5.5.2 Catch-ups for individuals aged 10 years and older**

For previously unimmunised individuals aged 10 years and older, a primary immunisation course consists of three doses of a diphtheria toxoid-containing vaccine at intervals of not less than four weeks (see Appendix 2). For children aged under 18 years, a booster dose is recommended at least six months after the third dose.

Children aged under 18 years may receive Tdap (funded from age 7 to under 18 years); adults aged 18 years and older may receive Td (funded) or Tdap (unfunded). Although Tdap and Td are not approved for use (registered) as a primary course, there are expected to be no safety concerns.

### **Dose intervals between Td and Tdap**

When Tdap is to be given to adolescents or adults to protect infants or other vulnerable individuals from pertussis, no minimum interval between Td and Tdap is required<sup>22, 23, 24</sup> – unless Tdap is being given as part of a primary immunisation course.

## **5.5.3 Booster doses for adults**

Studies overseas show that many adults lack protective levels of the antibody, and this has led to concern about waning immunity and recommendations for booster doses beyond childhood (see also section 5.3.2). Most authorities recommend maintaining diphtheria immunity by periodic reinforcement using Td.<sup>8</sup> A single booster dose of Tdap induces seroprotective levels of antibodies to diphtheria and tetanus in virtually all children and adolescents, and in a high proportion of adults and elderly individuals at approximately one month post-vaccination, irrespective of their vaccination history.<sup>25</sup>

In New Zealand, following the dose of Tdap at age 11 years, booster doses of Td are recommended (the vaccine is funded, but not the administration) at ages 45 and 65 years. These age-specific recommendations may facilitate the linkage of adult immunisation to the delivery of other preventive health measures.

## **Booster doses before travel**

If someone is travelling to an area endemic for diphtheria, or there is another reason to ensure immunity, a booster dose is recommended (but not funded) if it is more than 10 years since the last dose. For website sources on travel vaccines, see Appendix 9.

### **5.5.4 Pregnancy and breastfeeding**

Pregnant women should receive a dose of Tdap (funded), recommended to be given from 16 weeks' gestation of every pregnancy. This should be given during each pregnancy<sup>26</sup> to protect the mother against pertussis and so that antibodies can pass to the fetus to protect the newborn (see section 4.1.2).

Td vaccine is not routinely recommended for pregnant women but it can be given under certain circumstances, such as when catch-up is needed for an under-immunised woman, or for management of a tetanus-prone wound<sup>26, 27</sup> (see section 19.5.5).

Td or Tdap vaccines can be given to breastfeeding women.<sup>27</sup>

### **5.5.5 (Re-)vaccination**

Diphtheria toxoid-containing vaccines are funded for (re-)vaccination of eligible patients, as follows. See also sections 4.2 and 4.3.

#### **DTaP-IPV-HepB/Hib (Infanrix-hexa) and DTaP-IPV (Infanrix-IPV)**

An additional four doses (as appropriate) of DTaP-IPV-HepB/Hib (for children aged under 10 years) or DTaP-IPV are funded for (re-)vaccination of patients:

- post-HSCT or chemotherapy
- pre- or post-splenectomy
- pre- or post-solid organ transplant
- undergoing renal dialysis
- with other severely immunosuppressive regimens.

Up to five doses of DTaP-IPV-HepB/Hib (for children aged under 10 years) or DTaP-IPV are funded for children requiring solid organ transplantation.

### **Tdap (Boostrix)**

An additional four doses (as appropriate) of Tdap (Boostrix) are funded for patients:

- post-HSCT or chemotherapy
- pre- or post-splenectomy
- pre- or post-solid organ transplant
- undergoing renal dialysis
- with other severely immunosuppressive regimens.

### **Td (ADT Booster)**

Td is funded for patients following immunosuppression.

## **5.6 Contraindications and precautions**

See also section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general contraindications for all vaccines.

### **5.6.1 Contraindications**

There are no specific contraindications to diphtheria vaccine (or Td/DT), except for anaphylaxis to a previous dose or any component of the vaccine.

### **5.6.2 Precautions**

See section 14.6.2 for precautions for pertussis-containing vaccines.

## **5.7 Expected responses and AEFIs**

Despite the widespread use of diphtheria toxoid, the 1994 Institute of Medicine review of vaccine reactions did not identify any reaction for which the evidence favoured or established a causal relationship with

diphtheria toxoid.<sup>28</sup> However, local and systemic reactions do occur with diphtheria toxoid-containing vaccine, especially when the infant vaccine is used in older children and adults. Mild discomfort or pain at the injection site persisting for up to a few days is common.<sup>29</sup>

See also sections 14.7 and 19.7 for expected responses and AEFIs with DTaP-IPV-HepB/Hib, DTaP-IPV, Tdap and Td.

## 5.8 Public health measures

It is a legal requirement that all cases of diphtheria be notified immediately on suspicion to the local medical officer of health.

Alert the laboratory that the sample is from a suspected case of diphtheria. All isolates of *C. diphtheriae* and *C. ulcerans* are notifiable until toxigenicity is determined, including cutaneous isolates. If the isolate is determined to be nontoxigenic (does not have the ability to produce diphtheria toxin), the case should be denotified.

All patients with *C. diphtheriae* or *C. ulcerans* isolated from a clinical specimen should be discussed with the medical officer of health urgently.

All contacts should have cultures taken.

### 5.8.1 Antimicrobial prophylaxis

All close contacts, after cultures have been taken and regardless of immunisation status, should receive:

- a single intramuscular dose of benzathine penicillin (450 mg for children aged under 6 years; 900 mg for contacts aged 6 years or older), or
- 7 to 10 days of oral erythromycin (children: 40 mg/kg/day; adults: 1 g/day, in four divided doses).

Benzathine penicillin is preferred for contacts who cannot be kept under surveillance.

In contacts with a positive culture: two follow-up cultures should be obtained at least 24 hours after completion of therapy. If cultures are

still positive, discuss further management with an infectious diseases physician. The primary healthcare practitioner should be kept informed of the management of contacts and laboratory results.

### **5.8.2 Vaccination of contacts**

All close contacts should also be offered a complete course of vaccine or a booster according to the following schedule.

- Fully immunised children aged under 10 years who have only received three doses of diphtheria toxoid-containing vaccine within the last five years: give one injection of a diphtheria toxoid-containing vaccine.
- Fully immunised individuals aged 10 years and older who have not received a booster dose of a diphtheria toxoid-containing vaccine within the last five years: if aged 10–17 years, give one injection of Tdap; if aged 18 years or older, give one injection of Td or Tdap; the latter is not funded (see section 5.5).
- Unimmunised individuals: see Appendix 2.

### **5.8.3 Exclusion of contacts**

Child contacts should be excluded from school, early childhood services and community gatherings until they are known to be culture negative. Adult contacts who are food handlers or who work with children should be excluded from work until known to be culture negative. Cases should be excluded from school until recovery has taken place and two negative throat swabs have been collected one day apart and one day after cessation of antibiotics.

For more details on control measures, refer to the ‘Diphtheria’ chapter of the *Communicable Disease Control Manual 2012*.<sup>30</sup>

## **5.9 Variations from the vaccine data sheets**

See section 14.9 for variations from the DTaP-IPV-HepB/Hib (Infanrix-hexa), DTaP-IPV (Infanrix-IPV) and Tdap (Boostrix) data sheets.

See section 19.9 for variations from the Td (ADT Booster) data sheet.

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