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## Impact of a three-dose diphtheria outbreak response immunization in East Java, Indonesia, 6 months after completion

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### ABSTRACT

Several outbreaks of diphtheria have occurred in the East Java Province of Indonesia since 2011. The last effort to stop the outbreak in the province was a three round outbreak response immunization (ORI) in 2018. The aim of this study was to evaluate the impact of the 2018 ORI in East Java province – 6 months following the completion of the program.

Surveillance data was collected for 6 month period, from January to June 2019. The source of data was the district health offices, hospitals, community health centers, and private physician and paramedic practices. The data included demographic characteristics, involved health facilities, patient immunization history, clinical signs and symptoms, some laboratory test results and other additional examinations. All cases were evaluated by the East Java Provincial Diphtheria Expert Committee and not based on the individual physician decision.

During the 6 month period, there were 97 diphtheria cases which approved by the Diphtheria Expert Committee. The reports came from 36 of 38 districts. One patient died, denoting a case fatality rate of 1%. The majority were 19 years of age or less, with uncomplete immunization. Patients above 19 years were 24%. Compared with 2017 (438 cases) and 2018 (310), 2019 saw a significant reduction in the number of reported cases. Only 4 positive culture results were collected (positivity rate 4,13%). Two patients had Mitis subtype and the other two had Gravis subtype. Diphtheria ORI in East Java had a significant impact during the first 6 months of 2019.

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### Introduction

Diphtheria is an infectious disease that killed many people especially in the prevaccine era.<sup>1–3</sup> Cases of this lethal disease are currently reported by only few countries, and a large number of cases are found in WHO-SEARO (World Health Organization – Southeast Asian Regional Office) countries, including Indonesia.<sup>4</sup> Sporadic outbreaks occur in other countries.<sup>5–7</sup>

Several outbreaks of diphtheria have occurred in the East Java Province of Indonesia since 2011, and approximately 1000 cases were reported in 2012.<sup>4,8,9</sup> East Java accounts for 85% of all diphtheria cases in Indonesia, the country that reports the second largest number of diphtheria cases worldwide. The outbreaks continue despite clinical and community interventions implemented by the Ministry of Health.<sup>9,10</sup>

Mass immunization is an effective response to outbreaks and has been successful in Russia, Laos, Nigeria, and Yemen.<sup>11–14</sup> In Indonesia, the Ministry of Health and the government of East Java conducted outbreak response immunization (ORI) in 2013 and 2018. The first ORI, which was conducted in 2013, had a planned 0-, 1-, and 6- month schedule with vaccinations planned in February, March, and August/September, and faced financial and political commitment problems. The second ORI

in 2018 offered three rounds-of vaccination in February, July, and November (0, 5, and 9 months, respectively).<sup>15</sup> This alternate schedule was implemented because of difficulties in vaccine preparation. The initial schedule was 0, 1, and 6 months, but the national vaccine company and the Ministry of Health could not guarantee delivery of the vaccine on time, and individual provinces could not determine the vaccination schedule on their own. Another problem was the time required to administer each vaccine dose. Some districts needed additional 2 weeks to complete the program.<sup>15</sup>

In this ORI, all 38 districts in the province participated, and the vaccination coverage was 97% for the first, 94% for the second, and 93% of the third round. Nearly 9 millions children – from 1 to 19 year of age – were vaccinated.<sup>15</sup> The aim of the present study was to evaluate the impact of the 2018 ORI in East Java province – 6 months following the completion of the program.

### Materials and methods

#### Surveillance data

Surveillance data was collected from district health offices, hospitals, community health centers, and private physician and paramedic practices by the East Java Provincial Health

Office, daily, weekly, and monthly from January 1, 2019 to June 30, 2019, depending on the volume of reported cases. The data included demographic characteristics, the involved health facilities, patient immunization history, clinical signs and symptoms, and laboratory and other relevant results. The standard regular reports were made weekly and monthly, by the district health offices. The monthly report, basically, summarizes all the items from weekly reports. If there was a new case, the district health office would make an additional report on that particular day, followed by serial daily reports for the next few days (those daily reports consist of all efforts regarding that specific patient, such as throat and nasal swab collection, contact tracing, and treatment provided). This study only used patients with verified diagnosis by the diphtheria expert committee. The data were reported as numbers and percentages, and the presentation and analysis were descriptive in nature.

### Microbiology laboratory

Mouth and nose swabs were obtained from patients and their close contacts. These specimens were collected at the hospitals or clinics by the local health officers. The specimens were placed in Amies transport medium (Deltalab SL) chilled to 2°C – 8°C and then transported to Balai Besar Laboratorium Kesehatan Surabaya (BBLK or Public Health Laboratory Surabaya) within 24 h. BBLK is the main diphtheria laboratory for East Java Province. It is one of two national reference laboratories for diphtheria in Indonesia. The specimens were cultured at BBLK in Hoyle medium for 24–48 h and then plated on Columbia agar. Gram-positive colonies were screened for *Corynebacteria* with API Coryne Test kits (Biomérieux).<sup>16</sup>

### Diphtheria expert committee

Clinical cases were reported by individual physicians to the provincial diphtheria expert committee by phone or e-mail. The members of the diphtheria expert committee evaluated a picture of the pseudomembrane and the patient history and sent their decision to the physician, together with their recommendations. Any significant changes in the patient status in the next 48 h were recorded and reanalyzed. If the committee decided that the clinical evidence was not compatible with diphtheria, then the health office dropped the case and specific treatment was not provided.

### Diphtheria diagnosis

The definitive diagnosis of diphtheria was based on the clinical evidence and microbiological examination results. As most cases were culture negative, the clinical status was crucial, and the diagnosis relied on the size, shape, and color of the pseudomembrane, clinical signs including fever, difficulty in swallowing, and bleeding, complications including bull neck, airway obstruction, myocarditis, nephritis, and neuritis; and, in some cases, the initial response to erythromycin. The expert committee also evaluated the immunization history of the patients.

### Diphtheria antitoxin (DAT)

Only cases approved by the expert committee could receive DAT. In East Java, distribution is managed by the Provincial Health Office, which requested and received DAT from the Ministry of Health.<sup>15</sup> DAT distribution has been managed at the national level since 2017. Before that time, limited supplies had resulted in a lack of DAT in the entire province.

### Diphtheria immunization coverage

Immunization coverage data were collected at the East Java Provincial Health Office, which is where most of the infectious disease surveillance officers were based. The data were collected monthly and yearly. The minimal target coverages for primary vaccination (DPT III) and the first booster (DPT IV) were 90%. The provincial health officer evaluated the coverage starting at the subdistrict level, for which the coverage target was also 90%. In Indonesia the national schedule includes a primary diphtheria vaccination series given at 2, 3, and 4 months of age and a first booster at 18 months of age.<sup>10,17</sup>

## Results

In the 6 months from January 1, 2019 to June 30, 2019, 172 suspected diphtheria cases were reported to the diphtheria expert committee and 97 were confirmed. Table 1 shows the numbers of suspected and confirmed diphtheria cases reported each year from 2016 to 2019. The majority of cases in 2018 and 2019 comprised children from 18 months to 7 years of age; 24% occurred in patients more than 19 years of age, and most were diagnosed in patients with incomplete immunization. Diphtheria cases were reported in 36 of the 38 participating districts. One patient died, denoting a case fatality rate (CFR) of 1%. Compared with 2017 and 2018, 2019 saw a significant reduction in the number of reported cases.

Figure 1 shows the age distribution of the patients with diphtheria in 2018 and 2019. In both years, the highest number of cases occurred in children from 18 months to 7 years of age. The immunization history of the children diagnosed with diphtheria is shown in Figure 2. Approximately 17% of the cases in 2018 and 21% of those in 2019 were diagnosed in children from 18 months to 7 years of age who received all the scheduled doses of vaccine. Only four cases (4.13%) in 2019

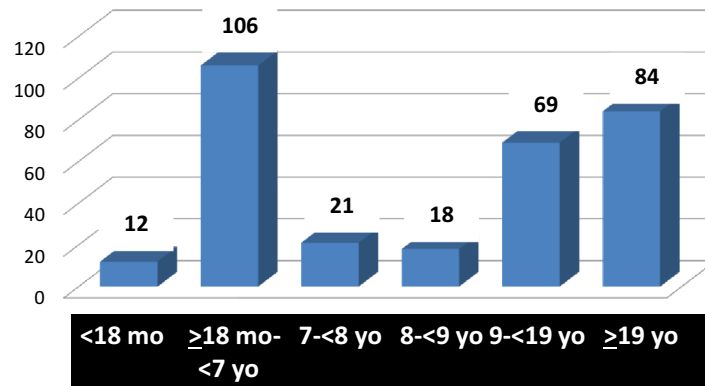
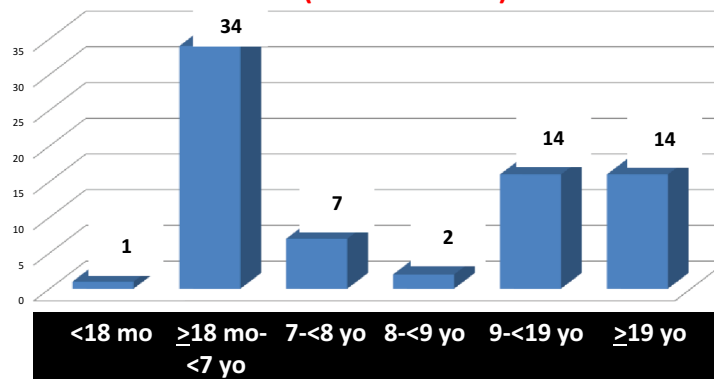
**Table 1.** Diphtheria cases in East Java Province in 2016–2019.

	YEARS			
	2016	2017	2018	2019 (Jan-June)
Suspected cases	343	640	756	172
Clinical case (approved by the expert committee)	*	438	310	97
Died patients	7	16	3	1
Average of cases per week	6.6	8.8	13.2 <sup>#</sup>	6.62 <sup>#</sup>
Positive microbiology culture			5.83 <sup>§</sup>	3.73 <sup>§</sup>
Districts involved	11	38	43	4
	32	38	38	36

\* = Approval by the expert committee was not applicable in 2016

# = Based on all suspected cases.

§ = Based on approved cases only.

**Diphtheria Cases with DAT by Age Group in East Java, 2018****2018****Diphtheria Cases with DAT by Age Group in East Java, 2019 (Jan – Jun 2019)****2019**

**Figure 1.** Diphtheria cases by age and treated with diphtheria antitoxin in 2018 and 2019.

were diphtheria culture positive. Two were mitis and two were gravis biotype cultures. *Corynebacterium diphtheriae* was isolated from patients and not from the contacts. The culture-positive patients had not been immunized. The patient who died had not received any immunization.

The immunization coverage in East Java Province between January 2016 until June 2019 is shown in Table 2. The average annual DPT III coverage for the whole province was stable, but differences in the number of districts with  $\leq 90\%$  coverage were observed in that interval. For DPT IV, both the average immunization coverage and the number of districts with  $\leq 90\%$  coverage were significantly better in 2018 (the ORI year) compared with the previous years.

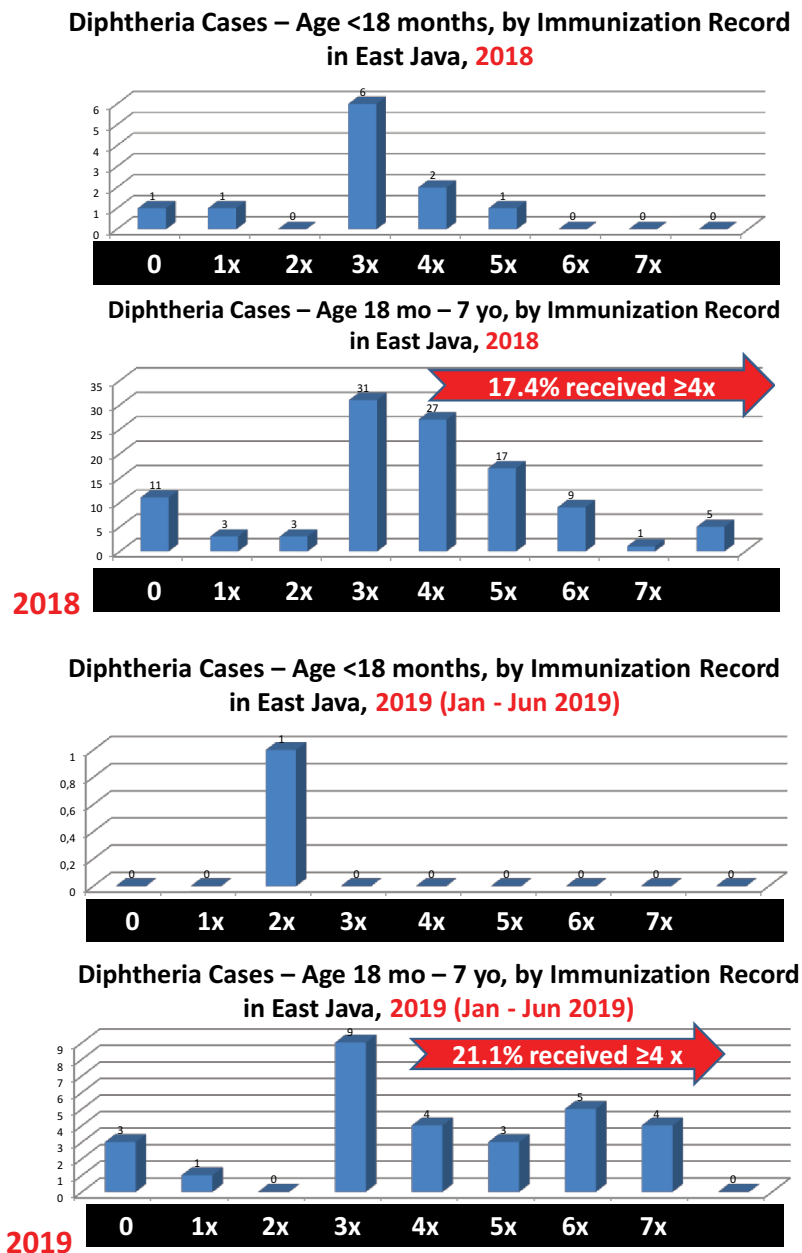
## Discussion

Diphtheria is under control in the developed countries, but remains a public health issue in some developing countries wherein yearly outbreaks occur.<sup>3-5,11,18-22</sup> Diphtheria

reappeared in Indonesia in 2005, and the incidence peaked in 2011–2012; however, the high number of diphtheria cases has not been satisfactorily resolved.<sup>8,10,23</sup> The largest diphtheria outbreak occurred in Russia between 1990 and 1998 and involved at least 150,000 patients, most of whom were adults. The outbreak was stopped by mass immunization, which was supported by many developed countries.<sup>12</sup>

The primary cause of diphtheria outbreaks is low vaccination coverage.<sup>3,6,14,20,24</sup> Overall immunization coverage of diphtheria, pertussis, and tetanus vaccination in Indonesia is not satisfactory.<sup>25,26</sup> There are also several pockets with very low coverage for various reasons including religious objection, fear of side effects, and lack of understanding.<sup>9,27</sup> Most outbreaks in East Java occur in the northern and eastern regions. Most people living in those areas are members of the Madura tribe.<sup>15,28</sup>

The latest diphtheria ORI was conducted by the Indonesian Ministry of Health in February, July, and November 2018, and it included several provinces but it was implemented in all



**Figure 2.** Confirmed diphtheria and number of immunizations received in children younger than 7 years of age by immunization status in 2018 and 2019.

districts only in East Java.<sup>15</sup> The ORI did not reach all ages. Priority was given to those who were 1–19 years of age because of financial constraints and weak political will. The country's financial condition indicated that the effort to overcome the epidemic by immunization was not a priority. However, local funding in East Java helped the ORI to reach all districts. Of approximately 9 million people who were targeted, coverage of the three doses was 97%, 95%, and 93%.<sup>15</sup> Coverage was relatively uniform throughout East Java, but several pockets in each region were relatively inaccessible. Additional difficulties during the ORI included delay in vaccine delivery and the rejection of some communities.<sup>15</sup>

We believe that the 2018 ORI succeeded in reducing the number of diphtheria cases and consider that one of the main reasons for this is that ORI covered a large number of children in East Java. The majority of cases recorded in 2019

included children who were not immunized, were not reached by the ORI, or had a history of incomplete immunization. Those older than 19 years of age accounted for many of the cases. During the January to June 2019 surveillance period, some patients with diphtheria were noted to be less than 19 years of age and had a good vaccination history, which requires further more investigation. The number of cases in children from 18 months to 7 years of age was relatively constant in 2018 and 2019. Most of those cases were diagnosed in children who had not received any doses of vaccine or who had not received all the required doses. Nevertheless, 17% (of the children in 2018) and 20% (in 2019) had histories of complete immunization. The use of an antibody test may be considered in future studies such as this one. The effectiveness of diphtheria vaccine is believed to be approximately 95%. Only approximately 5% of cases would

**Table 2.** Immunization coverage in East Java Province from January 2016 until June 2019.

DESCRIPTIONS	2016 (Jan-Dec)	2017 (Jan-Dec)	2018 (Jan-Dec)	2019 (Jan-Jun) <sup>b</sup>
Average immunization coverage (DPT III) <sup>a</sup> for the whole province	96.67%	93.91%	98.82%	47.02%
Range of immunization coverage (DPT III) among districts	70.83%-106.29%	73.13%-105.69%	76.87%-110.04%	34.68%-54.54%
Average immunization coverage (DPT IV) <sup>a</sup> for the whole province	74.26%	76.99%	98.93%	38.62%
Range of immunization coverage (DPT IV) among districts	28.12%-108.61%	29.91%-108.61%	63.65%-142.98%	15.82%-51.72%
Number of districts with full report of the immunization coverage	38/38 (100%)	38/38 (100%)	38/38 (100%)	38/38 (100%)
Number of districts with immunization coverage (DPT III) <90%	6/38	12/38	4/38	12/38
Number of districts with immunization coverage (DPT IV) <90%	28/38	33/38	8/38	33/38

<sup>a</sup>Regular schedule for infants in Indonesia: DPT I (2 months), DPT II (3 months), DPT III (4 months), DPT IV (18 months).

<sup>b</sup>Cumulative DPT immunization coverage target for January until June 2019 was 45% (=half of the target for 12 months (90%)). The target for DPT IV immunization coverage for 6 months was also 45%.

be expected to have a complete immunization history.<sup>29–31</sup> ORI can end diphtheria outbreaks but to be successful it needs strong financial support and the commitment of all stakeholders in the country.<sup>3,14,20</sup> For some countries, international support has been very important.<sup>12</sup>

The high incidence of suspected diphtheria in 2018 and 2019 reflects the ability of medical personnel to find cases characterized by membranes in the oral cavity. This was previously an issue, especially when the outbreaks began appearing, as some cases of tonsillar and pharyngeal diphtheria were easily confused with other diagnosis, especially by medical personnel with limited experience. Many differential diagnoses are based on the presence of a white membrane, such as other types of bacterial tonsillitis, fungal infections, herpetic ulcer, infectious mononucleosis, and post tonsillectomy condition.<sup>1,2,32–35</sup>

Usually, there were no significant fluctuations in the number of diphtheria cases except for January until March 2018, when the number of reported cases increased after the Ministry of Health declared a national diphtheria outbreak in December 2017. This was, possibly, the result of mass publicity and societal panic.<sup>15</sup>

Since 2016, the overall DPT III coverage in East Java Province has been >90%, but several districts did not reach that target (Table 2). The ORI may have helped to close the gap in many of those pocketed areas. The national DPT coverage in 2018 was only 61.3%.<sup>10</sup> Most reported cases involved patients older than 18 months of age, which is consistent with the lack of DPT booster coverage. This ORI provided a DPT booster. The DPT IV coverage in East Java was relatively low in 2017, but many districts met the 2018 target because of the ORI. Twelve districts failed to reach the target of 90% DPT IV coverage in 2017, but only four failed to do so in 2018 (Table 2). DPT IV coverage is one of the main weaknesses in the national immunization program.

Microbiological culture is the strongest proof of diagnosis, but only four cases in East Java during the study period were culture positive. The percentage of culture positive clinical diphtheria in East Java has never been more than 10% since 2011.<sup>9</sup> Improvements in the quality and number of reference laboratories may succeed in closing the gap. Both mitis and gravis biotype cultures were found in this study. Historically, the majority of biotypes in East Java have been the mitis biotype, with the gravis biotype found only in certain areas. The gravis biotype has a much higher level of antibiotic resistance than the mitis biotype, which makes it more difficult to treat.<sup>36</sup>

Before 2017, the diagnosis of diphtheria did not require confirmation by the expert committee. The policy was changed because the supply of diphtheria antitoxin (DAT) is limited and the Indonesian Ministry of Health had centralized the distribution of this drug. Priority was given to confirmed cases of diphtheria which now requires a decision from the expert committee. Only cases approved by the expert committee will get the DAT. Changes in the diagnosis requirements have also played a role in the reduction in the number of cases but when the confirmed cases in 2018 and 2019 are compared, the policy change alone is not likely by itself responsible for the decrease. This indicates that ORI has played a crucial role in the reduction.<sup>15</sup>

To the best of our knowledge, this report is the first evaluation of the effectiveness of ORI in East Java. Observations will continue for at least the next 3–4 years.

The primary limitations of the study include the short period of evaluation time as 6 month maybe insufficient. Moreover, our evaluation was started only 1 month after the completion of ORI. However, many children in our region were not naive and had already received one or two doses of diphtheria vaccine. For this group, one or two rounds of ORI were enough to raise the immunity. However, other children only completed the primary vaccination but not the first booster; for this group the ORI might play a significant role. The evaluation after ORI needs quite a sufficient time. We plan to continue the evaluation for at least 1 year. The second limitation of this study was regarding the accuracy of the diphtheria diagnosis, which initially relied on the clinical performance of the clinicians. However, the evaluation of all reported cases performed by the expert committee would hopefully be able to reduce the uncertainty of the diagnosis. Moreover, the performance of the microbiological diagnostic procedure was another limitation of the study because there were only four positive results. The improvement of the yield of microbiological cultures is very important. Since 2012, our reference laboratory has been supervised by Diphtheria Reference Laboratory in Collindale, United Kingdom.<sup>8</sup>

ORI is not a substitute for routine immunization and cannot be expected to produce short-term results. Improved routine immunization is required to achieve sustainable results.

In conclusion, diphtheria ORI in East Java had a significant impact during the first 6 months of 2019, and the evaluation is ongoing. Further evaluation of the case contacts is warranted.



## Abbreviations

BBLK: Balai Besar Laboratorium Kesehatan Surabaya; CFR: Case Fatality Rate; DAT: Diphtheria Anti Toxin; ORI: Outbreak Response Immunization

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## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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