SIX MONTH EVALUATION AFTER THREE ROUND DIPHTHERIA OUTBREAK RESPONSE IMMUNIZATION IN EAST JAVA

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Intorduction

Several outbreaks of diphtheria have occurred in the East Java Province of Indonesia since 2011, and approximately 1000 cases were reported in 2012.[1-3] 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 depite clinical and community interventions implemented by the Ministry of Health.[3-5]

The Ministry of Health and the government of East Java conducted outbreak response immunization (ORI) in 2013 and 2018. The first ORI, which was cond ucted 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). All 38 districts in the province participated, and the vaccination coverage was 97% for the first, 94% for the second, and 93% oh the third round. Nearly 9 millions children – from 1 to 19 year of age - were vaccinated.[6] 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 offices, hospitals, community health centers, and privae physician and paramedic practices by the East Java Provincial Health Ofiice, daily, weekly, and monthly from Januari 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 characteristics of close contacts were also obtained. The data were reported as numbers and percentages, and the presentastion and analysis were descriptive in nature.

Microbiology laboratory

Mouth and nose swabs were obtained from patients and their close contacts at Balai Besar Laboratorium Kesehatan Surabaya (BBLK), one of the two national reference laboratories for diphtheria in Indonesia. The specimens were placed in Amies transport medium (Deltalab SL) chilled to 2°C – 8°C and transported to BBLK within 24 h. 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 (Biomerieux).[7]

Diphtheria Expert Committee

Clinical cases were reported by individual physicians to the provincial diphtheria expert committee by phone or email. 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. Immunization history was a significant risk factor.

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% occured 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 occured in children from 18 months to 7 years of age. The immunization history of the children diagnosed with diphtheria is shown in Figure 2

and confirms that 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 had not received all the scheduled doses of vaccine. Only four cases (4.13%) in 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.

Discussion

Diphtheria is under control in the developed countries, but remains a public health issue in some developing countries wherein yearly outbreaks occur.[1,5,8-14] 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.[2,4,15] The largest diphtheria outbreak occured in Russia between 1990 and 1998 and involved at least 150,000 patients, most of whom were adults. The outbreak was stopped by by mass immunization, which was supported by many developed countries.[16]
The primary cause of diphtheria outbreaks is low vaccination coverage.[8,12,17-19] Overall immunization coverage of diphtheria, pertussis, and tetanus vaccination in Indonesia is not satisfactory.[20,21] There are also several pockets with very low coverage for various reasons including religious objection, fear of side effects, and lack of understanding.[3,22] Most outbreaks in East Java occur in the northern and eastern regions. Most people living in those areas are members of the Madura tribe.[6,23]
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 districts only in East Java.[6] 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%.[6] Coverage was relatively uniform throughout East Java, but several pockets in each region were relatively inaccesible. Additional difficulties during the ORI included delay in vaccine delivery and the rejection of some communities.[6]
The 2018 ORI succeeded in reducing the number of diphtheria cases. 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 be expected to have good a complete immunization history.[24-26] ORI can end diphtheria outbreaks but to be successful it needs strong financial support and the commitment of all stakeholders in the country.[8,12,19] For some countries, international support has been very important.[16]

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.[27-32]

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.[3] Improvements in the quality and number of reference laboraries 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.[33]

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.[6]

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 accuracy of the diagnosis of diphtheria, which must be strengthened, and the improvement of the yield of microbiological cultures.

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.

As the conclusion, Diphtheria ORI in East Java had a significant impact during the first 6 months of 2019. The evaluation is ongoing. More complete evaluation of the case contacts is required.

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Table 1. Diphtheria cases in East Java Province in 2016-2019

	YEARS			
	2016	2017	2018	2019 (Jan-June)
Suspected cases	343	640	756	145
Clinical case (approved by the expert committee)	*	438	310	76
Died patients	7	16	3	1
Average of cases per week	6.6	8.8	13.2#/5.83$	6.77#/3.68$
Positive microbiology culture	11	38	43	4
Districts involved	32	38	38	36

*= Approval by the expert committee was not applicable in 2016
= Based on all suspected cases
$ = Based on approved cases only

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

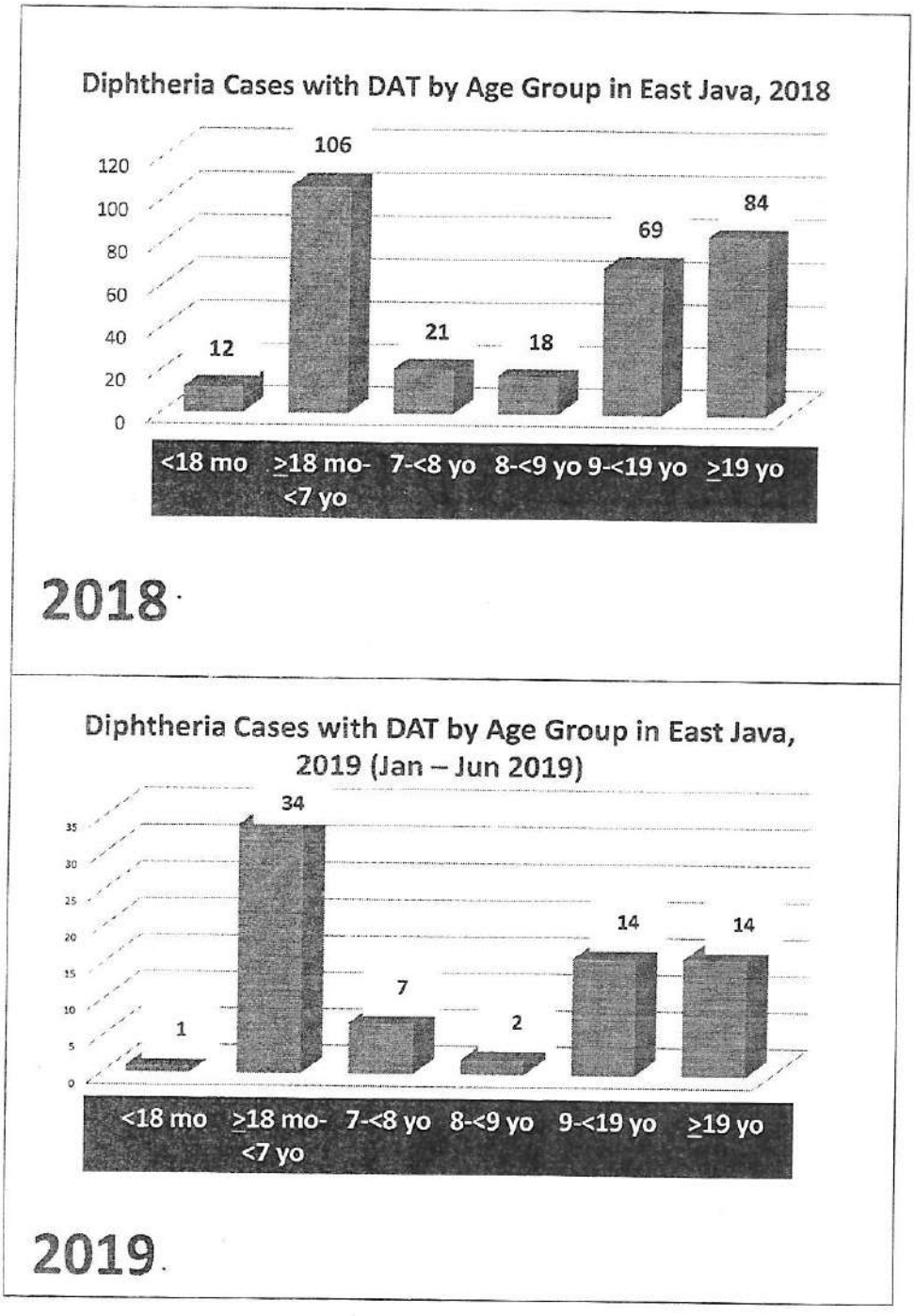

Figure 2. Confirmed diphtheria and number of immunizations received in children younger than 7 years of age by immunization status in 2018 and 2019