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Two Clustering Diffusion Patterns Identified from the 2001–2003 Dengue Epidemic, Kaohsiung, Taiwan

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Abstract. This study analyzed the spatio-temporal patterns of 4,587 (94% of the total) confirmed dengue cases in Kaohsiung and Fengshan Cities (a two-city area) that occurred in Taiwan from 2001 to 2003. The epidemic had two simultaneous distinct diffusion patterns. One was a contiguous pattern, mostly limited to 1 km from an initial cluster, reflecting that there was a rapid dispersal of infected *Aedes aegypti* and viremic persons. The second followed a relocation pattern, involving clusters of cases that diffused over 10 weeks starting from the southern and moving to the northern parts of the two-city area. The virus from one clustering site jumped to several distant areas where it rapidly dispersed through a series of human–mosquito transmission cycles to several localities. In both patterns, transmission of disease quickly enlarged the epidemic areas. Future dengue control efforts would benefit from a timely syndromic surveillance system plus extensive public education on how to avoid further transmission.

INTRODUCTION

In the last few decades, there have been an increasing number of dengue epidemics in tropical and subtropical countries.[1] The transmission of dengue occurs primarily through infected female mosquitoes, *Aedes aegypti* or *Aedes albopictus,* which acquire the virus when taking blood meals from infected humans.[2] *Ae. aegypti,* which has a multi-meal feeding behavior on several people, is most often found among humans in urban dwellings.[3,4] Because dengue virus infection can be mildly/atypically symptomatic, even asymptomatic, it is likely that disease can spread silently and can remain in a community without being noticed.[5,6] As a result, wherever there were clustering dengue cases confirmed for consecutive weeks, there might have been the possibility that infected mosquitoes are present but undetected.[7] Therefore, if the spatial and temporal factors of the clustering of dengue cases were better understood, we could more efficiently prevent and control the transmission of dengue virus.

Between 1987 and 2001, there were epidemics of dengue in Taiwan almost every 3–4 years. They started from imported cases, and most of the epidemics were small-scale involving zero or a small number of cases of dengue hemorrhagic fever (DHF).[8] From 2001 to 2003, however, epidemics of dengue/DHF predominantly caused by dengue virus serotype 2 (DENV-2) occurred in the two-city area of Kaohsiung and Fengshan, where Taiwan experienced its largest and most severe epidemic in 60 years (Figure 1). Previous studies, using geographical point pattern analysis to study outbreaks in other countries, have shown that dengue cases tend to be clustered either within the same household or in nearby neighborhoods.[3,4,7,9] The aim of this study was to characterize in detail the spatio-temporal patterns of the spread of dengue cases in this two-city area during Taiwan's 2001–2003 dengue epidemic. We showed that dengue case clustering occurred in a contiguous pattern at the community level and in a relocated pattern after the virus had rapidly dispersed on large geographical areas.

MATERIALS AND METHODS

Study areas, dengue cases, and surveillance of dengue in Taiwan. Kaohsiung City is the second largest metropolitan area in Taiwan. Neighboring Fengshan City, which has become an extension of Kaohsiung City, is located directly to its east (Figure 1). In 2002, the population density of the two-city area was ~10,200 people/km^2. According to the data from the late 1990s, ~4.90 million trips were made per day within Kaohsiung City and between the two cities.[10] In addition, there were no obvious differences between the percentage of people living in business districts and residential districts in the two cities. In fact, many people in these two cities may live in one city and work in the other, increasing the frequency of movement of the dengue-infected persons between the two cities during outbreak periods. In addition, there are many night markets, outdoor markets in Fengshan City where susceptible people gather together and transmission of the virus is facilitated. Therefore, this two-city area was the major focus of virus dispersal and the infections there accounted for as much as 78% of all dengue cases occurring during Taiwan's 2001–2003 dengue/DHF epidemic.

In dengue surveillance, most vector surveillance efforts are implemented more intensively once dengue cases are reported or confirmed in Taiwan.[11] Human surveillance of dengue cases includes passive reporting and semi-active surveillance. Local physicians at all hospitals and clinics in the two-city area are required to report any suspected dengue cases and to collect plasma/serum samples from them for laboratory confirmation during epidemic periods.[12] Another semi-active surveillance system for dengue in Taiwan searching for neglected or hidden dengue cases requires local public health

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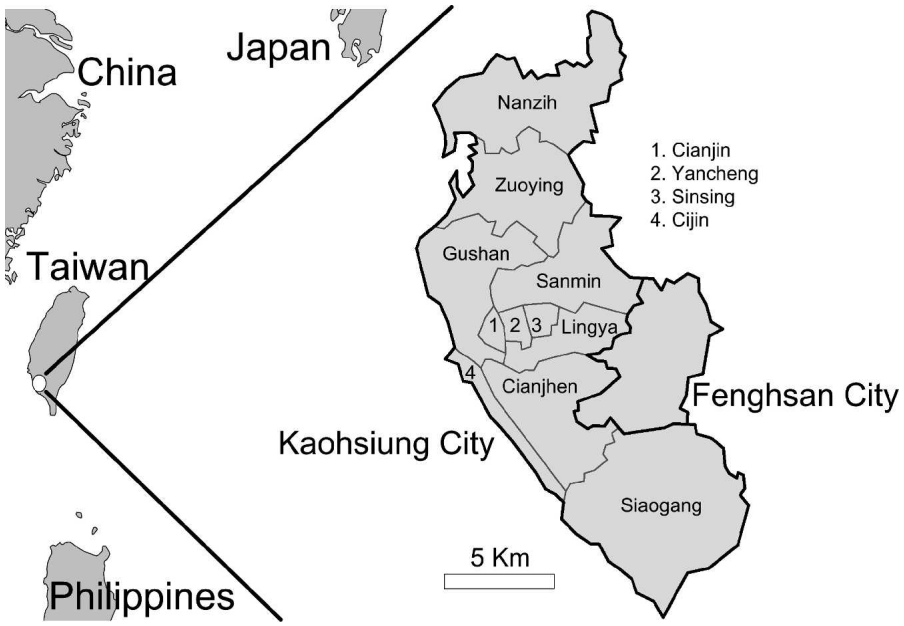

FIGURE 1. The two-city area (Kaohsiung City and Fengshan City) located between 22°30′30″ to 45′30″ N, and 120°14′30″ to 23′30″ E in southern Taiwan. Names of the districts are labeled.

personnel to obtain blood samples of all fever and febrile cases located within a 500-m radius of infected residences, workplaces, and other places with epidemiologically linked to confirmed dengue cases (http://www.cdc.gov.tw). Clinical definition of dengue cases in our study was based on the same definitions of DF and DHF used by the World Health Organization. To further simplify our analysis, only total laboratory confirmed dengue cases were studied. Dengue-positive cases were confirmed by one of the three laboratory methods: molecular diagnosis by reverse transcriptase-polymerase chain reaction (RT-PCR) using dengue virus–specific primers,[2] serologic testing for dengue IgM seropositive but Japanese encephalitis IgM seronegative,[13] or virus isolation in C6/36 mosquito cells.[14] Because the collection of mosquito density data during that time in Taiwan was not a random sampling, we preferred to use better quality data on dengue cases for further diffusion analysis. If the dengue cases in certain areas persisted for > 2 weeks, it was very likely that infected mosquitoes had not been controlled successfully. Therefore, we analyzed the geographical distribution of 4,869 confirmed dengue cases caused by dengue virus serotype 2 (DENV-2) in the two-city area and summarized the weekly data from the first case (May 5, 2001) to the last case (March 7, 2003) for a total of 96 weeks.

Spatial and temporal pattern analyses. We mainly focused our analysis of spatio-temporal patterns of transmission on the residences of dengue cases because we assumed that dengue virus was transmitted domestically and peridomestically in those localities where there were many confirmed dengue cases. To do this, we used point pattern analysis, documented in literature,[3,4] to summarize our weekly data from the first case (May 5, 2001) to the last case (March 7, 2003).

To identify spatial clusters of dengue cases and to estimate density surfaces of the clusters on the map, we used a two-step method involving K-order nearest neighbor analysis[15,16] and kernel estimation.[16] K-order nearest neighbor analysis was used to determine the most appropriate bandwidth size,[17] which could reflect the geographic range of infected mosquitoes that might cause dengue cases. A diagram (Figure 2) using all Kth nearest neighbor index values was plotted on the *y*-axis, and the mean distances between each tested case and the K-order nearest neighbor were plotted on the *x*-axis. The closer the K-order nearest neighbor index was to zero, the more clustering there was in a tested area. Based on a plateau between 450 and 550 m in the K-order nearest neighbor index plot (Figure 2), we estimated that 500 m (*x*-axis value before the slope went flat) was the most appropriate bandwidth. To avoid the boundary effect in spatial clustering detection, the circular border correction method in Crimestat II was applied.[15] Next, we used the appropriate bandwidth as the circular searching radius (500 m) to generate spatial surface of dengue risk map from those cases throughout the 96-week

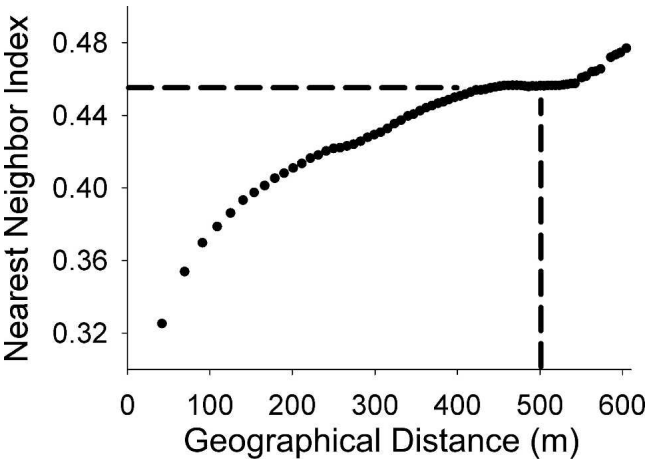

FIGURE 2. The K-order nearest neighbor analysis showed the relationship between the nearest neighbor index and observed distance (m) of the Kth nearest neighbor. A 500-m bandwidth was selected from a plateau (450–550 m).

epidemic by using kernel density estimation on ESRI ArcGIS version 8.3. Weighing for the neighboring dengue cases while scanning all the epidemic areas, we were able to obtain information on the density of clustering.

The resulting density surfaces, mapped by kernel estimation, were categorized into four different cluster levels per unit of square kilometers (Figure 3B and C): 1) ≤ 2.5, 2) 3.75–12.5, 3) 12.5–125, and 4) ≥ 125 dengue cases. In this study, we defined "cluster areas" as having > 12.5 cases/km^2. Based on this definition, we identified six dengue clustering

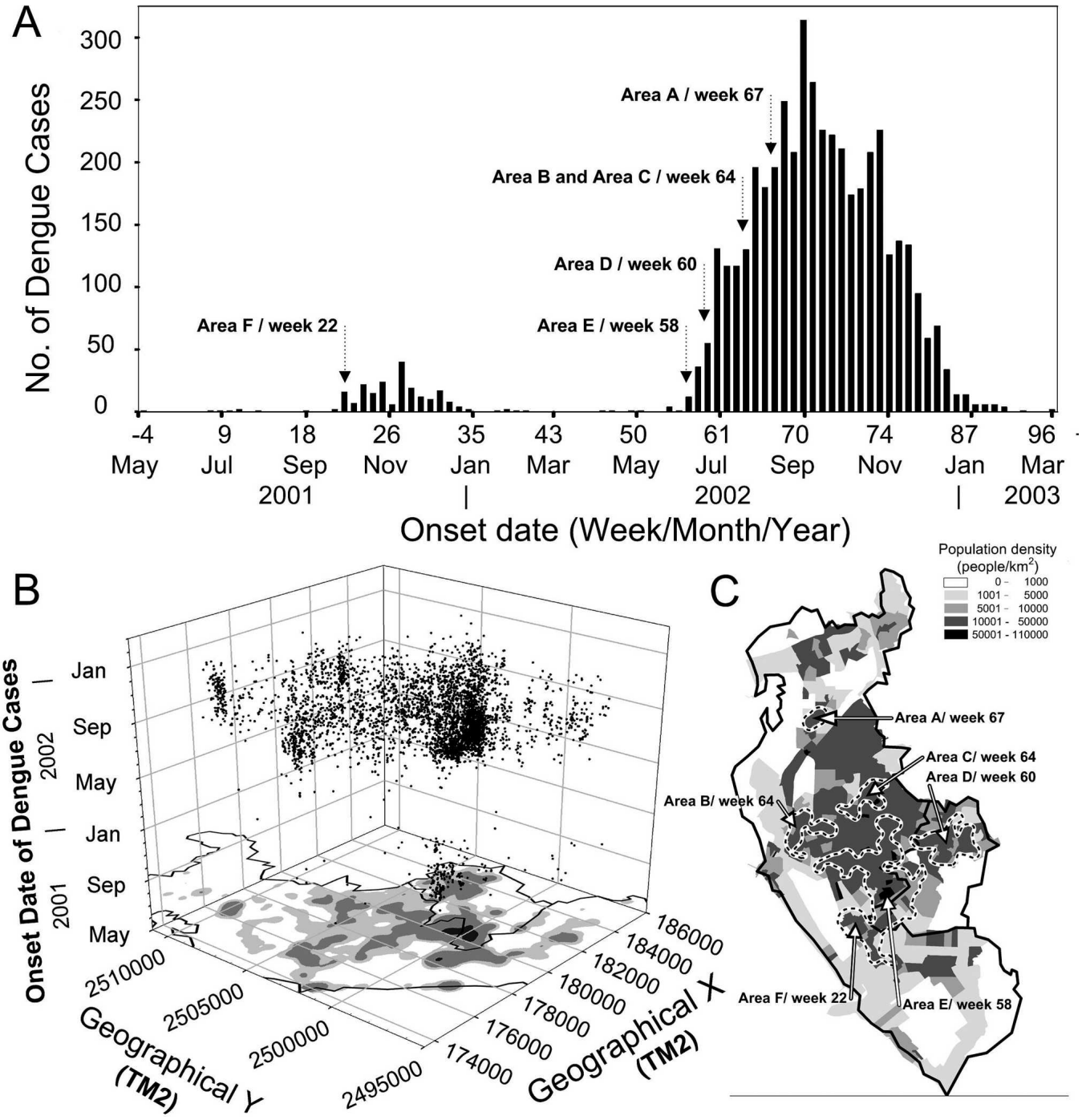

FIGURE 3. Temporal and spatial distribution of confirmed dengue cases in the two-city area in Taiwan. **A**, An epidemic curve of weekly confirmed dengue cases between May 5, 2001 (Week 1, first identified case) and March 1, 2003 (Week 96). Arrows indicate the appearance of clustering cases in selected areas. **B**, Spatio-temporal clusters of dengue cases. Axes x and y are geographical coordinates in Taiwan datum (transverse mercator projection). Onset date of each dengue case is labeled as z-axis. Two-city map projected on x–y plane and grayscale was categorized as four different levels according to the number of dengue case per unit of 0.8 km^2: (1) < 3 cases (no color), (2) 3–10 cases (light gray color), (3) 11–100 cases (gray color), and (4) $\geq$ 101 cases (deep gray color). **C**, Kernel estimated density map of > 10 dengue cases per unit of 0.8 km^2 is shown within the zebra line. Population density was presented as the right top corner (in gray to black colors). Arrows indicate the location of the first clustering cases appearing in each of the selected areas by onset week.

areas (Figure 3A–F) and further studied their directions of diffusion (Figure 3C).

RESULTS

Case georeferencing. The addresses of the 4,869 confirmed dengue cases whose residence information could be found in Taiwan's residence database were converted to geographic coordinates. After excluding those whose addresses we could not find, we were left with 4,587 confirmed dengue cases (94%), which we used to characterize the patterns of disease diffusion.

The accuracy of geocoding was tested by randomly selecting 454 cases to be compared using a GPS receiver (Garmin, Taiwan), digital aerial photographs (supported by the Aerial Survey Office, Forest Bureau, Council of Agriculture, Taiwan), and the Web GIS household registration database provided by the Kaohsiung Civil Affairs Bureau web site (http://address.kcg.gov.tw). After eliminating seven outliers (0.2%) resulting from inconsistencies between the GPS receiver and aerial photographs, we found the mean error for 447 residential addresses to be 31.5 m, which was acceptable for data analysis.

Demographics of the dengue cases. Based on WHO criteria, 4,245 (92.5%) of the 4587 Kaohsiung's confirmed dengue cases were DF cases and 342 were DHF cases. The male-to-female ratio was 0.867 (2,130/2,457). Age was a significant confounder in dengue cases, with most being > 45 years old (2,523 [59.4%] of DF cases, 271 [79.2%] of DHF cases, and 60.9% of total dengue cases; Table 1).

Epidemic curve and place. There were two dengue epidemic waves in the two-city area between 2001 and 2003 (Figure 3A). A small initial wave involving 217 cases (5% of the total cases) occurred between May 2001 and February 2002. A larger-scale epidemic wave involving 4,361 cases followed between May 2002 and February 2003. Viewed from the macro level (A–F) and identified by nearest neighbor analysis, we found six statistically significant dengue clustered areas (Figure 3C). Eighty-five percent of the cases in the first wave occurred in a single focal area (Area F), whereas 83% of the cases in the second wave were spread over Areas A–F, a much wider pattern (Figure 3B and C). During the first 10 weeks of 2002, dengue cases spread from the south to the north in the A–E epidemic areas (Figure 3C, arrows). Although 89% of the A–F areas were located in the places where population densities were > 5,000 inhabitants/km^2 (Figure 3C, the zebra line), not all high population areas in Kaohsiung had a clustering of dengue cases during this epidemic. Only 27% of the areas with > 5,000 inhabitants/km^2 had pockets involving > 12.5 clustering dengue cases/km^2. As indicated by dashed lines in Figure 4, the incidence of dengue cases in initial weeks embedded in the E and F epidemic areas overlapped with the most severe regions where the cumulated density of dengue cases during the entire epidemic period was > 125 cases/km^2, represented by deep gray in Figure 4.

TABLE 1

Distribution of sex and age of the total dengue cases in the epidemic of DF/DHF in Kaohsiung, 2001–2003

	Dengue cases*	
	Total number (*N*)	Percentage (%)
Sex		
Male	2,130	46.4
Female	2,457	53.6
Age (years)		
< 15	202	4.4
15–29	697	15.2
30–44	894	19.5
45–59	1,525	33.2
≥ 60	1,269	27.7
Total	4,587	100

* Dengue cases included both DF and DHF cases.

Geographical clustering cases and dynamic dispersion. Although we regarded the 2001–2003 epidemic of dengue/DHF as one epidemic period because only one serotype (serotype 2) and one genotype of dengue virus was isolated from indigenous dengue cases based on high identity of viral sequences,[18] we preformed a detailed analysis of the spatial diffusion patterns of the dengue cases in these two waves. To closely study the spread of the dengue cases in the abovementioned six different clustering areas over time by weekly basis, we designated the week in which the index case occurred in 2001 as Week 1, the following week as Week 2, and so on until Week 96, when the last dengue case ended in March 2003.

Wave 1: initiating diffusion of dengue cases in Area F (Weeks 21–26, October–November 2001). To find out whether there was a consistent dispersal pattern in all six areas (A–F), we generated spatial risk surfaces to study the weekly dynamic changes of dengue cases during the initial 5 weeks immediately after the first appearance of each cluster in each of the cluster areas (A–F). The first epidemic wave started with the appearance of a single sporadic case (Week 21 of the epidemic) in 2001 before the first clustering in Qianzhen District (Figure 4: Area F). One week later, a cluster of 16 dengue cases was identified in Area F covering a 750-m-diameter area, where the clustering persisted the following week (Week 23). An additional seven cases occurred in the same 750-m area as the previous week. In Weeks 24–25, most dengue cases (20 of the 22 cases in Week 24 and 14 of the 15 additional cases in Week 25) also occurred in the same areas. By Week 26, we found 25 additional cases and identified other new cluster areas, forming a long axis extending ~1.6 km. These changes made the risk area more peanut-shaped. In fact, 21 of these additional 25 cases (84%) in Week 26 indeed occurred within the identified risk areas from previous weeks (areas within the risk areas representing as dashlines in Weeks 22–25 as shown in Figure 4), although the index case of these new areas involving dengue cluster cases was identified in Week 24, 2 weeks prior. Apparently, dengue cases at Week 26 involving not only 84% of them originated from previous weeks maintaining the first cluster but also forming the second cluster as peanut-shaped, implying that the newly formed second cluster was relocation diffused from the first cluster. In brief, Area F was found to have concentric circles expanding outward from Week 22 to Week 26 of 2001 with overlapping and expanding boundaries centered on a single epidemic focus, which was initially identified in the 2001. There was an average of 23 new cases/km^2/wk during this time.

Wave 2: initiating diffusion of dengue cases in Area E (Weeks 58–62, June–July 2002). In the second wave of the epidemic, the average number of cases in Area E increased dramatically from < 7 (Week 58 in Figure 4: Area E) to 34

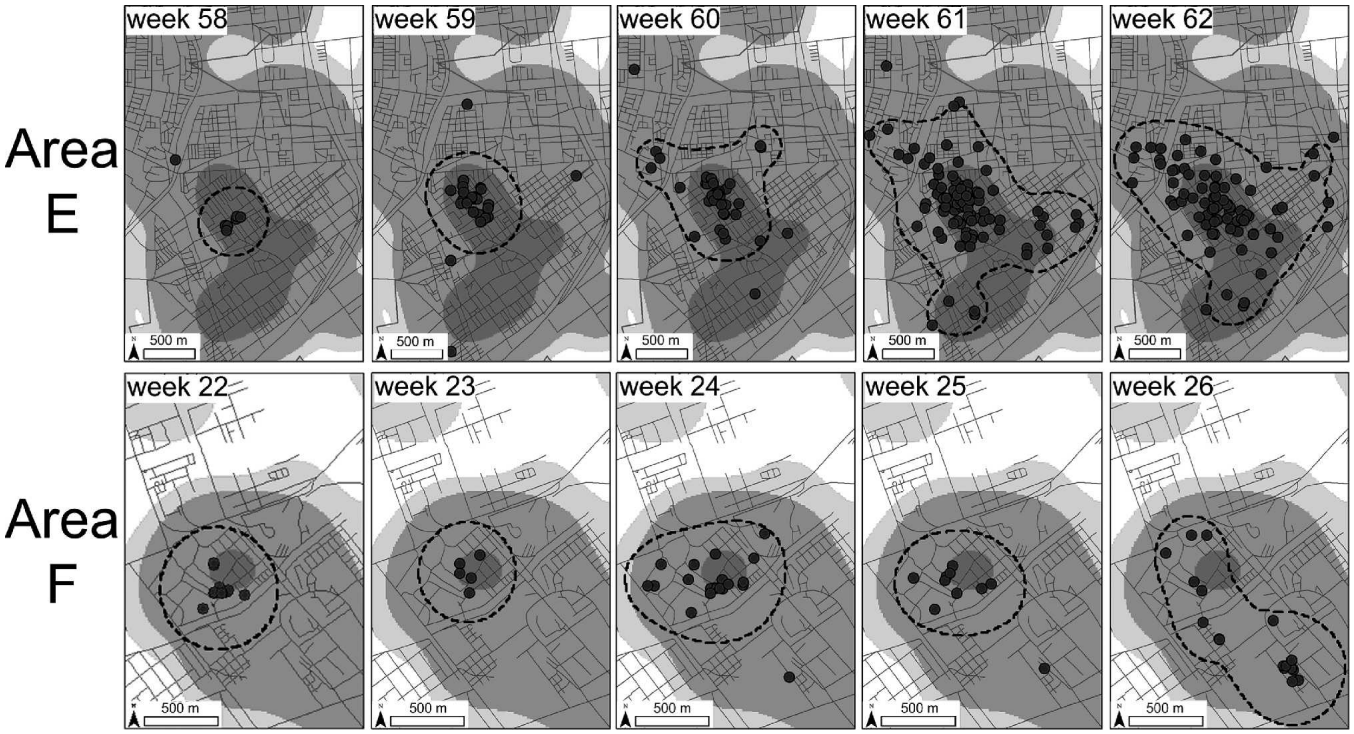

FIGURE 4. Map of spatio-temporal clustering cases in the initial 5 weeks since the first cluster was identified in Areas E and F. Locations of dengue cases were labeled as block dots. Dash-line circled risk area has > 2 cases/0.8 km^2/wk. Shade area is defined as > 2 cases (light gray), > 10 cases (gray), and > 100 cases (deep gray) in 0.8 km^2 between 2001 and 2003.

cases/km^2/wk (Week 61 in Figure 4: Area E). Between June 10, 2002 and July 12, 2002, the risk area grew outward at an average rate of 19 km^2/wk (Figure 4: Area E). This quickly expanding pattern of dense case distribution made Area E the largest cluster area involving the most cases. In that area, 10 of the 12 cases clustered in the initial week of the second wave (Week 58 of the epidemic period) were located within the 700-m-diameter dashed-line circle. Thirty-one of the 36 new cases that occurred the following week (Week 59) were clustered around the same center as the previous week. The focal area was identical, and the risk area had expanded by 2 km in diameter. This pattern of diffusion in Area E was quite similar to that identified in Area F. By Week 60, relocation diffusion, a phenomena characterized leaving the original area behind to move to new areas,[17] had occurred. Forty-two of the 52 (80.8%) new cases were clustered. In fact, 18 of the 42 cases (42.8%) shared the same addresses or lived in neighboring buildings. They neighbored the cases of Week 58 and also imparted the same living space, which included outdoor day markets, parks, night markets, and areas with high mosquito indices. This made clustering likely to occur. At this time, we found two new clusters located in the northern parts of the two-city metropolitan area, giving the whole risk area a "Mickey Mouse" shape (Area E in Figure 4). In Week 60, sporadic cases located in the southern part of the Mickey Mouse appeared outside of the estimated risk area (e.g., occurring relocation diffusion again). These new areas of sporadic cases were found to be part of even larger cluster areas in the following 2 weeks. In Week 61, new cases increased sharply. Most (106 of 131; 80.9%) were clustered. For Area E, a critical point was reached after Week 60, when the number of cases began increasing sharply.

Small-scale diffusion in other areas. In contrast, the transmission of dengue in Areas A–D (Figure 5) was quite restricted, staying under 1 km in diameter. Most of the risk areas stayed near the center of the initial outbreak site, showing contiguous diffusion following a concentric circle spreading pattern in Areas A, C, and D but not in Area B (Figure 5). In Area B, where dengue cases spread in a small-scale relocation diffusion pattern, the outbreak started with one initial clustering. That cluster disappeared and reappeared again with a new focus.

DISCUSSION

A large-scale epidemic of dengue reflects the continuous existence of several series of transmission chains.[1,19] Spreading can be explained by the movement of either infected mosquitoes or infected people through a neighborhood.[3–5,20–25] In this study, we identified two different spatial diffusion patterns: contiguous diffusion and relocation diffusion. The range of dengue virus distribution began to spread quickly through the two-city area, with relocation diffusion occurring simultaneously with contiguous diffusion. Most importantly, if the number of human–mosquito transmission cycles in a cluster was large enough to successfully create another cluster, a large-scale epidemic could rapidly occur. Hence, relocation diffusion contribute greatly to the increase scale of an epidemic because it facilitates the spread of the virus to different localities (Figure 3).[26] The change from contiguous diffusion to relocation diffusion in our study could have been because the original contiguous diffusion pattern might have reflected the direction of the outward expanding activity among those infected vectors serving as "the source of the infection" for 2–3 weeks. There could have been an increase

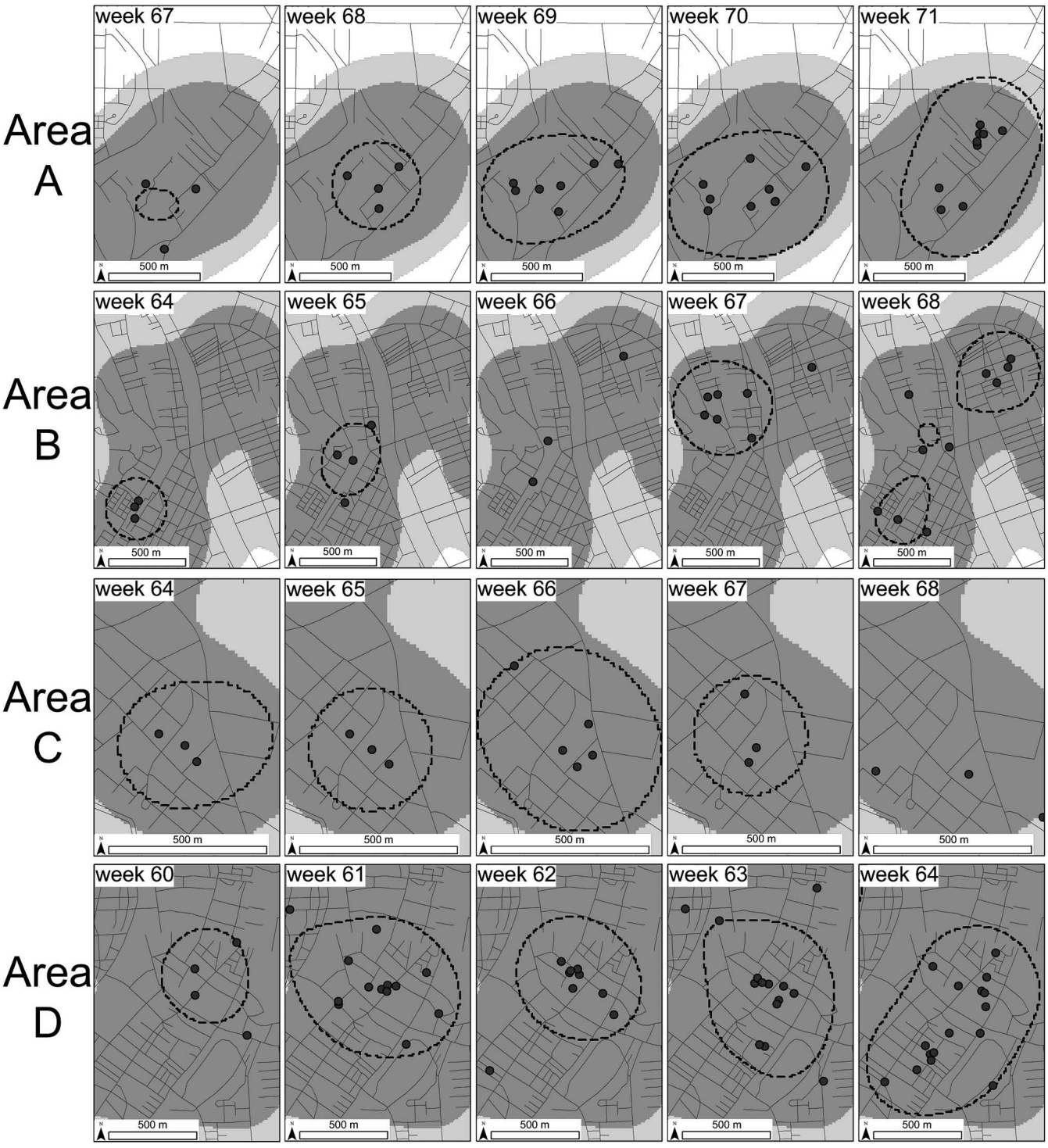

FIGURE 5. Map of spatial-temporal clustering cases in the initial 5 weeks since the first cluster was identified in selected areas. **A–D**, Locations of dengue cases were label as black dot. A risk area has circled in dash-line as > 2 cases/0.8 km^2/wk. Shade area is defined as > 2 cases (light gray) and between 11 and 100 cases (gray) in 0.8 km^2 between 2001 and 2003.

in herd immunity, limiting the size of the original/earlier epidemic site(s). This could have been followed by the migration of dengue virus infected persons carrying the virus to other areas resulting in "relocation pattern." If this is how the change in diffusion pattern occurred, it would mean that early dengue control would not only limit the size of contiguous diffusion but also minimize the possibility of relocation diffusion and reduce the number of other possible epidemic sites.

The two patterns of diffusion occurred in areas with high population densities (Figure 3C). Densely populated areas are at increased risk of importing the dengue virus and have enough susceptible people to facilitate contiguous diffusion.

Furthermore, dengue virus serotype 2 (DENV-2) has seldom been involved in large epidemics in Kaohsiung before 2001, suggesting that almost none of the population there had built up sufficient herd immunity. This would mean that population density of those susceptible Kaohsiung's residents to DENV-2 would be large in 2002. Together these findings, combined with the fact that the risk ranges in this study were all greater than the mosquito flight range, suggest that the large-scale spread of dengue cases may be more a result of movement of infected people than the movement of the infected mosquitoes. However, the diffusion of dengue was restricted in areas with low population densities, slowing the limited spread of the virus and thus reducing the possibility of large-scope spread there. To reduce the chances of Taiwan becoming a dengue endemic/hyperendemic area,[27] prevention and control of dengue should emphasize more on surveillance of cases with dengue-like illness integrated with mosquito surveillance and source reduction of mosquito breeding sites.

A detailed study of spatial clustering is helpful when attempting to understand the mechanisms underlying the spread of an epidemic. In the contiguous diffusion we observed, the range of risk to dengue illness in the initial 5 weeks was limited geographically to 0.5–2.0 km in diameter, depending on time and place. Therefore, like many other infectious diseases, dengue decreased susceptibility and increased herd immunity, signifying a reduction in transmission and limiting transmission from a particular cluster. The diffusion started from an original focus area and spread outward in each epidemic region, A, D, E, and F (Figures 4 and 5), indicating that the unidentified or uncontrolled source of infection continued to disseminate the virus in the local community after it was introduced. The contiguous pattern may reflect the active dispersal of infected *Ae. aegypti*[3–5,19–24] and their multi-meal behavior.[28] However, our case clustering pattern of concentric circles extended beyond the area of individual house, but, like the observations from different countries, we found the dispersal range of mosquitoes to be usually limited to a few hundred meters.[24,25,29–31] According to Gubler and others,[1] dengue cases are presented by a scattering of infected mosquitoes because dengue viruses in the earliest cluster cases are primarily transmitted to mosquitoes and require an extrinsic incubation period (EIP) to be transmitted to the next person. As the clustering of cases continued in our study, a series of human–mosquito transmission cycles occurred in the two-city clustering areas, which might have gone beyond the clustering ranges of *Ae. aegypti*[22] and dengue cases[3,4] reported previously. In fact, our clustering of dengue cases in the initial 5 weeks after the establishment of the first cluster overlapped with the epidemic foci of Areas A to F, which accounted for 83–85% of cumulative cases. Again, these results re-illustrate the importance of analyzing initial case clusters.

Human activities, daily movements, and social networks were found to be important in our six epidemic areas when there was relocation diffusion. No or only very few sporadic cases were found in these areas between the previous epidemic wave and newly arising one within 4 km, a distance longer than the flying range of mosquitoes, again suggesting that infected persons might have played a predominant role in speeding up the dispersal of the virus, similar to several literature findings.[24,25,29,30] Interestingly, the accelerated geographic spread of cases in A–F areas occurred just 1 week before the sharp increase in clustering shown in the epidemic curve. The undiagnosed asymptomatic dengue virus infections or unrecognized dengue cases with mild symptoms could also have made possible the silent spread of dengue virus and undetected persistence of transmission in that locality.[5,7] Therefore, broader surveillance is needed to minimize possible total infection in the communities where dengue viruses are circulating. When doing this, whenever new cases are confirmed or clustering cases are identified in initial weeks of an outbreaks, public health officials must keep in mind that reinforced surveillance is needed to closely watch all possible common exposure sites, particularly common mosquito breeding areas or common areas where humans mingle, including parks, day/night markets, bus stops, school playgrounds, and temples. To do this, geographical information systems (GISs) can be used to locate problems and prevent a possible series of transmissions in a timely manner. This would keep the disease contained within a residence or with the activity area where the index case occurred and prevent it from spreading to surrounding areas. An enlarged cluster diameter (Area E) indicates a failure to control (Figure 4). This 2002 epidemic was not contained until the collaboration efforts between local environment protection agency and local department health began working simultaneously door-to-door to reduce mosquito breeding sites in different areas. This only occurred after we used GIS to show government officials that their failure to control this boundary area was a result of two administration units (Kaohsiug City and Fenghsan City) in the junction of the two-city using different control dates. In other words, Kaohiung City's mosquito control campaigns forced those infected mosquitoes to escape and fly toward Fenghsan City (locations of the two cities as shown in the Figure 1). Their failure to coordinate resulted in the need for much more manpower to do integrated vector control for a larger epidemic.

Besides the contiguous diffusion among epidemic areas of A, D, E, and F, we also observed relocation diffusion at the community level in Areas B (Weeks 66–67), E (Weeks 59–60 and Weeks 60–61), and F (Weeks 25–26). It took ~2–4 weeks for the disease to be spread by humans through relocation dispersion to distant areas where new epidemic foci were created. This time interval was close to or slightly longer than the time period needed for one cycle of human–mosquito–human transmission.[29] The dengue viruses spread throughout the two-city metropolitan at a speed of 2.5 km/wk, which was much slower than that reported from Thailand (148 km/mo)[32] and its rapid cross-country dispersion during World War II.[1] Therefore, speed and scale of human transmission is erratic, regardless of whether spread starts from on case or from several sporadic cases imported from different areas.

This study has several limitations. The actual number of dengue cases may have been underestimated. This underestimation might have been because some asymptomatically infected people did not seek medical care or because infected people with mild symptoms/signs were overlooked by unsuspecting physicians. Our follow-up serologic surveillance in Kaohsiung found that the seroprevalence rate of dengue virus infection in schoolchildren was low (C-C King, personal communication), and most dengue cases or dengue virus–infected individuals were adults with lower asymptomatic ratios rather than children with much higher asymptomatic ratios as identified in most Southeast Asian countries.[33] Dengue cases may

also have been underreported either because the physician, being less public minded, did not report suspect cases or because patients kept the information secret to avoid authorities from spraying their houses with insecticide and reduce the possibility that neighbors would complain of the smell. Another limitation might be that, in this study, we focused on dengue cases and paid no heed to environmental and climatic factors, which have also be known to contribute to persistent community transmission. Despite these limitations, our main conclusion regarding the two diffusion patterns of dengue cases from this large-scale epidemic shown in this study remain true and relevant. We believe that further research on integrating case findings with environmental conditions and social factors would be very helpful to explain the mechanism underlying the dynamic transmission of the virus between mosquitoes and human activities.

Viruses carried from areas of intensive transmission can be readily transmitted to neighboring areas as well as any part of the world. The success of dengue control in many countries can be jeopardized by the reliance on insecticide spray alone, inappropriate use of insecticide, insecticide resistance,[34] a low awareness or lacking of cooperation by local residents regarding the reduction of mosquito breeding sites at the community level, and undetected cases.[11] The method used in this study, which analyzed the number of dengue cases by spatio-temporal clustering, should help in evaluating the effectiveness of control efforts and in locating hidden mosquito breeding sites,[32,35,36] particularly during the first 2–3 weeks after a cluster appears. Once dengue cases exceed a certain threshold, large-scale transmission chains in the risk areas will make it more likely for infected humans and mosquitoes in one locality to carry dengue viruses to other localities. As dengue cases are expanding globally and most mosquito control programs are reactive,[11] there is an increasing need to establish a cross-country dengue surveillance network,[37] improve mosquito surveillance, and advise dengue patients to restrict their activities to be better interrupt the transmission chains from human to mosquitoes, minimize the multiple introductions of dengue virus, and improve the health of people wordwide.[1] To prevent and control dengue more effectively in Taiwan and elsewhere, we recommend establishing a surveillance system capable of collecting data on major risk factors before and during an epidemic using GIS to monitor possible spatial trends in the spread of the virus. Such a system can begin to provide rapid and timely feedback so that public health agencies can more efficiently formulate and implement health policies that can respond to an ongoing epidemic.

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