Tuberculosis situation among tribal population of Car Nicobar, India, 15 years after intensive tuberculosis control project and implementation of a national tuberculosis programme
M.V. Murhekar,1 C. Kolappan,2 P.G. Gopi,3 A.K. Chakraborty,4 & S.C. Sehgal5

Objective To assess the tuberculosis (TB) situation in the tribal community of Car Nicobar island 15 years after the national TB programme was implemented in this area after an intensive phase of TB control in 1986.

Methods The entire population of Car Nicobar was enumerated through a house-to-house survey. Children aged ≤ 14 years were tuberculin tested and read for reaction sizes. Individuals aged ≥ 15 years were asked about the presence of chest symptoms (cough, chest pain, and unexplained fever for two weeks or longer and haemoptysis), and sputum samples were collected from patients with chest symptoms. Sputum samples were examined for presence of acid-fast bacilli.

Findings Among the 4543 children enumerated, 4351 (95.8%) were tuberculin tested and read. Of the 981 children without bacille Calmette–Guérin scars, 161 (16.4%) were infected with TB. A total of 77 cases who were smear-positive for TB were detected from among 10 570 people aged ≥ 15 years; the observed smear-positive case prevalence was 728.5 per 100 000. The standardized prevalence of TB infection, annual risk of TB infection, and prevalence of cases smear-positive for TB were 17.0%, 2.5%, and 735.3 per 100 000, respectively.

Conclusion The prevalence of TB infection and smear-positive cases of TB increased significantly between 1986 and 2002. Such escalation took place despite the implementation of the national TB programme on this island, which was preceded by a set of special anti-TB measures that resulted in sputum conversion in a substantially large proportion of the smear-positive cases prevalent in the community. The most likely reason for the increase seems to be the absence of a district TB programme with enough efficiency to sustain the gains made from the one-time initial phase of special anti-TB measures. High risk of transmission of TB infection currently observed on this island calls for a drastic and sustained improvement in TB control measures.

Keywords TB, Pulmonary/epidemiology/prevention and control/ethnology; National health programs/organization and administration; Ethnic groups; Medically underserved area; India (source: MeSH, NLM).

Mots clés Tuberculose pulmonaire/épidémiologie/prévention et contrôle/ethnologie; Programme national santé/organisation et administration; Groupes ethniques; Géographie; Zone sous-équipement médical; Inde (source: MeSH, INSERM).

Palabras clave TB pulmonar/epidemiología/prevención y control/etnología; Programas nacionales de salud/organización y administración; Grupos étnicos; Geografía; Área sin atención médica; India (fuente: DeCS, BIREME).

Introduction Pulmonary TB continues to be an important public health problem in developing countries, even though requisite technology for its control is available (1, 2). This is mainly attributed to the operational problems of implementing the long-term control programme. India contributes almost one-third to the global burden of TB (3). A national TB programme has been implemented across India since 1962. Its performance in terms of case-finding and treatment, however, has not been as expected (4).

Considerable scientific information is available about the efficiency of TB control policy in isolated communities. The level of risk of TB infection and its decrease in the Eskimos of Alaska and Greenland is a specific example of TB control in...
isolated communities (2). The incidence of bacteriologically positive cases of TB in these communities was halved every three years, while the annual risk of infection among under-five-year-olds was also dramatically reduced (2). This is strikingly different from the almost static risk of infection observed over 10–15 years in some parts of India (5). The results achieved in these isolated communities were possible through intensive case finding, treatment, and prophylactic measures not followed elsewhere.

This method was adopted by the Andaman and Nicobar Administration for TB control among a population of the Nicobarese tribe that resides in the remote and isolated Car Nicobar island in the Bay of Bengal in 1986 in the form of a set of specialized activities, termed by them as “intensified TB control programme” (6). Briefly, the project included identification of all patients with chest symptoms (chest symptomatics) in the entire population of Car Nicobar. All identified chest symptomatics were subjected to chest radiography and sputum examination.

Tuberculin testing of children aged ≤14 years showed that 10% of the children not vaccinated with bacille Calmette–Guérin (BCG) were infected before implementation of the programme. A total of 39 (409.9 per 100 000) cases that were sputum smear-positive (S+) and 75 (788.3 per 100 000) radiologically active cases that were sputum smear-negative (X+) were identified from people aged ≥15 years. In total, 35 children with tuberculous cervical adenopathy were diagnosed during the survey. All of the S+ cases detected during the survey were treated with nine-month, short-course chemotherapy and X+ cases with a two-drug regimen. The cases of glandular TB in children identified by house-to-house survey were treated appropriately. Chemoprophylaxis with isoniazid was given to unaffected children aged 5–14 years for six months. Of the 39 S+ cases identified, three died before they completed the short course of anti-TB treatment and one patient defaulted; 33 (94.3%) of the 35 remaining S+ cases were still sputum negative on completion of treatment. Of the 75 X+ cases, two defaulted during the 18-month treatment period and five died before treatment was completed; of the 68 remaining X+ cases, 67 (98.5%) remained sputum-negative on completion of the treatment (6, 7). The annual incidence of new S+ cases was a third of the initial prevalence, which was as expected (5, 6).

After a lapse of 16 months, tuberculin testing was repeated in samples from seven of the 15 villages. No fresh infection was noted among those who were tuberculin-negative during the first round of tests. New TB infections in the community were interpreted as being prevented during the period after the concurrent case-finding treatment programme supported by chemoprophylaxis (8). The results achieved, as evaluated after 16 months, were thus found to be in concordance with the objectives of set of specialized one-time activities adopted under the project (2). At the end of this special project, anti-TB activities in this island were carried out through the implementation of a national TB programme, with the hypothesis that it would ensure long-term and sustainable objectives.

This study aimed to assess the impact of the above project on the TB situation on Car Nicobar 15 years after completion of the “intensified control programme”. The findings are reported in terms of prevalence of TB infection, annual risk of TB infection, and prevalence of TB cases compared with the values in 1986.

Material and methods

Study area

Andaman and Nicobar islands, Union Territory of India, is an archipelago of more than 300 islands in the Bay of Bengal. As well as immigrants from mainland India, these islands are home to six primitive tribes, which constitute about 10% of the population. More than 98% of the tribal population is constituted by the Nicobarese — a mongoloid tribe. For administrative purposes, the islands are divided into two districts: Andamans and Nicobars. Car Nicobar is the administrative headquarters for Nicobar district and has the largest size of tribal population in the Andaman and Nicobar islands.

Every Nicobarese village has a village chieftain. These chieftains and the religious leaders have influence over the population and exercise control in liaison with the chief captain. The people generally practise living together in large joint families called “tuhet”. This comprises a principal homestead and large lineage group that resides in the individual houses and huts. Tuhet indicates an extension of a family and is the unit of all social life in Car Nicobar.

Field procedures

The present study was carried out in 2001–02 to assess the impact of the strategy of the initial phase of an intensified control programme followed by a routine national TB programme for nearly 15 years, as pursued in this population. The same survey methods used during the project in 1986 were adopted for the present study to cover the entire population that resided in the 15 villages of the island (6). The field and technical staff for the survey were trained at Tuberculosis Research Centre, Indian Council of Medical Research, Chennai.

Before the survey started, a meeting of the chief captain, village chieftains, tribal council members, and medical officers in the island was organized. The purpose and methods of the survey were explained, and their cooperation for the survey was sought. During initiation of the survey in a village, a meeting with village chieftains and tuhet heads of that village was organized. The purpose of the survey was explained and the cooperation of all villagers was requested.

A sketch map of the village that indicated the lanes and numbers of houses in each lane was drawn during the planning visit to the village. A house-to-house census was undertaken to register all of the residents of the village. These visits were carried out systematically during the evening and night hours to ensure the presence of as many inhabitants as possible. The data were collected from the individuals and recorded in a pre-coded format.

The presence of chest symptoms such as cough, chest pain, and unexplained fever for two weeks or longer and haemoptysis was elicited from all people aged ≥15 years. Two sputum samples — one spot and one overnight — were collected from the chest symptomatics. Sputum-smear-positive cases were referred to Civil Hospital, Car Nicobar, for anti-TB treatment.

Registered children aged ≤14 years in a village were assembled at a central place in the village and subjected to tuberculin skin testing. The BCG scar status was recorded for each child after both shoulders were examined. If a scar was present but did not possess the characteristics of a BCG scar, it was recorded as doubtful. Each child, irrespective of BCG scar status, was injected intradermally with 0.1 ml of tuberculin containing...
1 tuberculin unit of PPD RT23 with polyoxyethylene sorbitan monoooleate (Tween 80) on the volar aspect of the left forearm. Children with fever or a history of skin rash in the recent past were excluded from testing. Informed consent was obtained from the parent or guardian of each child.

The test reactions were read about 72 hours later by a reader without knowledge of the child’s BCG scar status. Margins of induration were identified by careful palpation, and the maximum transverse diameter of induration was measured with a transparent scale. The size of the reaction in millimetres was dictated to the reader’s secretary for recording. The presence of vesicles, bullae, and necrosis, if any, were also recorded. In a sample of tested children, readings were repeated by the same reader and also by a second reader in every village to measure the intra- and inter-reader variability (data not presented).

Statistical methods
The data were double entered using Foxpro software and were validated. The secondary mode of the distribution was identified from a histogram that showed the frequency distribution of reactions sizes in millimetres. The number of children infected was calculated with the “mirror image technique”: by doubling the number of children with reaction sizes larger than the mode and adding to the number of children at the mode.

The annual risk of TB infection was computed from the prevalence of infection (P) with the equation below, where a is the mean age of the children test read.

\[
\text{Annual risk of TB infection} = 1 - (1 - P)^{1/a}
\]

Chi square (χ²) test with continuity correction was used to test the significance of differences between proportions, with \(P<0.05\) as significant. The data were analysed with Epi-Info software (version 6.04).

The prevalence of infection in the 1986 survey was calculated with the antimode method (6). The data from 1986 were reanalyzed with the “mirror image technique” for comparability with the present report. Table 1 gives the data from the 1986 and present survey, both on the basis of earlier methods of computation, to place these rates in the perspective of the annual risk of TB infection reported in earlier studies in India (5, 9).

Results
Population and coverage
A total of 15,575 people were enumerated from 15 villages of Car Nicobar, which included 4543 (29.2%) children aged \(\leq 14\) years. The age pyramid of the population enumerated during this study and the earlier project in 1986 is presented in Fig. 1. Evidence of comparative ageing of the population was present during this study (χ² = 433.5, \(P<0.001\)). Because of this, standardized infection and disease rates were used for comparison between the two surveys. Table 2 shows the coverage of different examinations.

Prevalence of infection
Of the 4351 children who were tested and read satisfactorily, 981 (22.5%) children were without a BCG scar. The frequency distribution of tuberculin reaction sizes among children without a BCG scar is presented in Fig. 2, which shows a bimodal distribution with the secondary mode at 19 mm.

Table 3 gives the prevalence of infection by age among children with and without a scar. The prevalence of infection among children without a BCG scar was 16.4%. The infection rates were found to increase linearly with age (χ² for trend 27.7, \(P<0.001\)). The standardized prevalence of infection was 17.0%, with the population distribution in 1986 as the standard. The prevalence of infection among children with a BCG scar was 13.9%; this was not significantly different from that among children without a scar (χ² = 3.71, \(P = 0.054\)).

Annual risk of Tuberculosis infection
The annual risk of TB infection based on observed prevalence of infection among children without a BCG scar was 2.4%, whereas that based on standardized prevalence was 2.5%. The annual risk of TB infection among children with a BCG scar was 2.0%.

Prevalence of disease
Of the 11,032 individuals aged \(\geq 15\) years, 10,570 (95.8%) were interviewed for the presence of chest symptoms and 965 (9.1%) had chest symptoms. A total of 77 S+ cases were detected, with a prevalence of 728.5 per 100,000 among those aged \(\geq 15\) years who were examined (observed prevalence) (Table 4). The estimated prevalence when adjusted to represent the registered population in all ages was 494.4 per 100,000 (with the assumptions that the population aged 0–14 years had no cases and the prevalence among the unexamined population was the same as in the examined group). The standardized prevalence in those aged \(\geq 15\) years was 735.3 per 100,000, with the population distribution in 1986 taken as the standard. The prevalence of S+ cases in those aged \(\geq 15\) years was significantly higher in 2001 (χ² = 8.85, \(P = 0.003\)) than in 1986.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Present survey (2001–02)</th>
<th>Previous survey (1986)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. analysed</td>
<td>No. infected*</td>
</tr>
<tr>
<td>0–4</td>
<td>360</td>
<td>46 (12.8)</td>
</tr>
<tr>
<td>5–9</td>
<td>331</td>
<td>79 (23.9)</td>
</tr>
<tr>
<td>10–14</td>
<td>290</td>
<td>121 (41.7)</td>
</tr>
<tr>
<td>Total</td>
<td>981</td>
<td>246 (25.1)</td>
</tr>
</tbody>
</table>

* Values in parentheses are percentages.
Discussion

A comprehensive TB survey of the entire population of an area with case-finding and treatment of the cases detected along with chemoprophylaxis for all unaffected children aged <15 years was effective in controlling TB in isolated communities (2). This method was adopted in the isolated tribal community of Car Nicobar in 1986 under a specially designed project not followed elsewhere in the country. The set of activities under the project was followed immediately by the introduction of a national TB programme in this community. The rationale behind the special project that preceded the introduction of the national TB programme was to identify as near to all infectious cases as feasible in the community and render them non-infectious so as to interrupt the transmission of infection. New cases that freshly appeared after the intensified programme (incidence) were expected to be identified and treated by the national TB programme. Vaccination with BCG and prophylaxis with isoniazid was intended to protect the children from infection, morbidity, and death. A repeat survey to study the extent of new infections in children carried out in seven of the 15 villages of the island 16 months later showed a “no incidence of infection situation” in the island (8). The present survey was carried out to assess the current situation with respect to TB in this island.

The tuberculin survey was restricted to children aged <15 years to measure the annual risk of TB infection. As in other parts of India, children were tested with 1 tuberculin unit PPD–RT23, as 1 tuberculin unit PPD–RT23 has been used exclusively in all tuberculin surveys in India in the recent past (10). Although some countries use 2 tuberculin units PPD–RT23, Chadha et al. showed that the sensitivity to detect infection was not significantly different between 1 tuberculin unit and 2 tuberculin units (10).

The BCG coverage among children in this survey was 77.5% (as assessed by the scar status). Although the analysis was restricted to children without a BCG scar (22.5%), this group may not necessarily be representative of all children in the community. The children without BCG scars may be at a higher risk of infection for reasons such as inaccessibility to health care facilities or because they are of lower socioeconomic status. Alternatively, they may be at a lower risk of infection if they happen to come from higher socioeconomic status, as the risk of TB is perceived to be lower among the latter. The group of children without a BCG scar, therefore, may be a biased sample. As the magnitude of bias is not known, both groups of children were analysed separately and are presented here. The results are not significantly different from one another; this indicates that the magnitude of bias is minimal.

Prevalences of infection derived from the mode method and annual risk of TB infection, which were 9.3% and 1.3% respectively, in 1986 were 16.4% and 2.4%, respectively, in 2001. This indicated worsening of the TB situation in the intervening period. The observed prevalence of disease among individuals aged ≥15 years increased from 409.9 per 100,000 in 1986 to 728.5 per 100,000 in 2001. The adjusted prevalence of disease in the total population was significantly higher in 2001 than 1986. The relation between annual risk of TB infection and adjusted prevalence of disease in the whole population was estimated as 1% annual risk of TB infection.

Table 2. Coverage of different examinations (2001–02)

<table>
<thead>
<tr>
<th>Examination</th>
<th>No. of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged ≤14 years</td>
<td></td>
</tr>
<tr>
<td>Enumerated</td>
<td>4543</td>
</tr>
<tr>
<td>Satisfactorily tested for tuberculin and treated</td>
<td>4351 (95.8)</td>
</tr>
<tr>
<td>Aged &gt;14 years</td>
<td></td>
</tr>
<tr>
<td>Enumerated</td>
<td>11032</td>
</tr>
<tr>
<td>Interviewed for presence of chest symptoms</td>
<td>10570 (95.8)</td>
</tr>
<tr>
<td>Identified as having chest symptoms</td>
<td>965 (9.1)</td>
</tr>
<tr>
<td>Sputum spears examined</td>
<td>952 (98.7)</td>
</tr>
</tbody>
</table>

* Values in parentheses are percentages.
equivalent to 206 S+ cases per 100 000 population in 2001–02 compared with 173.6 cases per 100 000 in 1986.

The observed trend of disease on Car Nicobar needs to be seen in light of its complete insularity — that is, no migration of population in and out of Car Nicobar. The dynamics of TB, as observed, thus has to be the consequence of developments indigenous to the island and the population that inhabits it, with the increase in case prevalence not the results of a process of migration. The rising trend observed in the present study in part could be the result of the ageing of the population (Fig. 2) or the prevalence of HIV, which has been reported to have been introduced to these islands and the Nicobarese tribe (11, 12).

The principal reason for worsening of the TB situation, however, could be attributed primarily to the poor performance of the national TB programme on the island. Such setbacks to an operationalized programme may not be unexpected, even for industrialized countries such as Japan (J3). Several reports of poor case-finding efficiency under a national TB programme have been published in India (4, 14). Of the maximal case finding potential of government health institutions, only one-third was achieved by national TB programmes. The performance of treatment activities in India also had been unsatisfactory under the national TB programme, with irregular drug supply and unsupervised chemotherapy (World Health Organization, South-East Asia Regional Office. TB programme review. New Delhi: WHO SEARO; 1992. Unpublished document). The situation may be even poorer in this isolated community because of poor connectivity with the main island, which contributes to lack of adequate supervision by programme officials and insufficient supply. In addition, no private practitioners or pharmacies are available on the island to provide alternative channels of treatment for TB patients not covered by the governmental machinery. The situation is different from other areas in India under the national TB programme in this respect.

A perusal of reports on district TB programmes since 1986 pertaining to this island shows that about 66% of S+ cases had completed treatment and 3.7% were dead. Case fatality among the diagnosed cases without programme intervention could be about 20%, as seen in the longitudinal survey carried out in India (15). Thus, the national TB programme on this island had succeeded in preventing deaths in an effective way. Mere prevention of death, however, hardly indicates a favourable epidemiological situation, as evident from the case in point: an escalation in case prevalence in the intervening period of 1986–2001.
Datta et al. showed that only 41% of the patients had been treated adequately under the national TB programme in the North Arcot district in Tamilnadu (16). The Tuberculosis Research Centre, Chennai, reported that the prevalence of S+ cases of TB showed little or no decrease over 15 years of follow up in the Chingleput district in Tamilnadu (17). Irregular and inadequate treatment under the control programme, postulated as taking place under the national TB programme in India, could be epidemiologically less favourable than the no treatment situation. It seems that irregular and incomplete treatment in nearly a third of S+ patients year to year in the only service set-up available in Car Nicobar might have caused accumulation of cases over time. The manner in which escalation of TB occurs in a community over a relatively short span of time is shown in the International Union Against Tuberculosis’s model of TB control (18). Apparently, accumulation of the incident cases after 1986 because of treatment failure could have resulted in the prevalence of TB cases doubling since 1986. The force of infection of the relatively fresh cases after 1986 must have caused the escalation in infection rate, as the new cases are supposed to be more infectious. The observed situation in this island is similar to the setback in the TB control efforts observed in the tribal population in Greenland, where the incidence of TB doubled over only eight years (19).

Conclusion

This study indicates an increase of TB among the Nicobarese tribe of Car Nicobar, despite the introduction of a national TB programme 15 years ago. The most probable reason for this seems to be the poor efficiency of the national TB programme. Implementation of a revised national TB control programme in this island, with DOTS strategy as soon as possible, is needed urgently. The data collected from this survey will be useful as baseline data to assess the impact of a revised national TB control programme on the TB problem on this island.

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Conflicts of interest: none declared.

Résumé

Situation de la tuberculose dans la population tribale de l’île de Car Nicobar (Inde) 15 ans après un projet de lutte intensive contre la tuberculose et la mise en œuvre d’un programme national de lutte antituberculeuse

Objectif Évaluer la situation de la tuberculose dans la communauté tribale de Car Nicobar 15 ans après la mise en œuvre dans cette île du programme national de lutte antituberculeuse à la suite d’une phase intensive de lutte antituberculeuse menée en 1986.

Méthodes La population de l’île de Car Nicobar a été intégralement dénombrée au moyen d’une enquête de porte en porte. Les enfants de 0-14 ans ont été soumis à un test tuberculique avec mesure du diamètre de la réaction. Les personnes de 15 ans et plus ont été interrogées quant à la présence de signes pulmonaires (toux, douleur thoracique, fièvre inexpliquée depuis au moins deux semaines et hémoptysie) ; un recueil de crachats a été effectué chez les patients présentant de tels signes et les bacilles acido-alcool-résistants ont été recherchés.

Résultats Sur les 4543 enfants dénombrés, 4351 (95,8 %) ont été soumis à un test tuberculique. Sur les 981 enfants ne présentant pas de cicatrice de BCG, 161 (16,4 %) étaient porteurs d’une infection tuberculeuse. Sur 10 570 personnes de ≥15 ans, 77 cas à frottis positif ont été détectés ; la prévalence observée des cas à frottis positif était de 728,5 pour 100 000 habitants. La prévalence normalisée de l’infection tuberculeuse était de 17,0 %, le risque annuel d’infection tuberculeuse de 2,5 % et la prévalence des cas à frottis positif était de 728,5 pour 100 000 habitants.

Conclusion La prévalence de l’infection tuberculeuse et des cas à frottis positif a augmenté de façon significative entre 1986 et 2002, malgré la mise en œuvre du programme national de lutte antituberculeuse sur l’île. Ce programme avait été précédé d’une série de mesures spéciales de lutte antituberculeuse ayant entraîné une négativation des frottis dans une proportion assez importante des cas à frottis positif trouvés dans la population. La cause la plus probable de cette augmentation semble résider dans l’absence d’un programme de lutte antituberculeuse au niveau du district suffisamment efficace pour maintenir les résultats de la phase initiale de mesures spéciales de lutte contre la tuberculose. Le risque élevé de transmission de l’infection tuberculeuse actuellement observé sur cette île appelle un renforcement énergique et durable des mesures de lutte antituberculeuse.
La tuberculosis en la población tribal de la isla de Car Nicobar (India), 15 años después del proyecto de control intensivo de la tuberculosis y de la aplicación de un programa nacional contra esta enfermedad

Objetivo Evaluar la situación de la tuberculosis en la comunidad tribal de la isla de Car Nicobar 15 años después de llevar a la práctica en esta área el programa nacional contra la tuberculosis tras una fase de control intensivo de la enfermedad en 1986.

Métodos Se procedió a hacer un recuento de toda la población de Car Nicobar mediante una encuesta casa por casa. Los niños ≤ 14 años fueron sometidos a la prueba de la tuberculina, determinándose el tamaño de la respuesta a ésta. A los individuos de más de 14 años se les preguntó si habían sufrido síntomas a nivel del tórax (tos, dolor torácico, y fiebre de origen desconocido durante dos semanas o más y hemoptisis), recogiéndose muestras de esputo en los casos en que así había sido. Dichas muestras fueron examinadas en busca de bacilos acidorresistentes.

Resultados De los 4543 niños contabilizados, 4351 (95,8%) fueron sometidos a la prueba de la tuberculina. De los 981 niños sin cicatrices por el bacilo de Calmette–Guérin, 161 (16,4%) presentaban la infección. Entre las 10 570 personas ≥ 15 años se detectaron en total 77 casos con baciloscopia positiva; la prevalencia observada de casos con baciloscopia positiva fue de 728,5 por 100 000. La prevalencia normalizada para la isla fue de 87,5 por 100 000. La prevalencia de casos con baciloscopia positiva fue de 2,5% y 735,3 por 100 000, respectivamente.

Conclusión La prevalencia de infección tuberculosa y de casos con baciloscopia positiva aumentó significativamente entre 1986 y 2002. Esa escalamada tuvo lugar pese a haberse puesto en marcha en la isla el programa nacional contra la tuberculosis, que fue precedido por una serie de medidas especiales contra la tuberculosis que se tradujeron en la conversión del esputo en una proporción considerable de los casos con baciloscopia positiva acumulados en la comunidad. La razón más probable del aumento parece ser la ausencia de un programa distrital contra la tuberculosis que fuese lo bastante eficiente para preservar los avances conseguidos gracias a la fase inicial única de medidas especiales contra la enfermedad. El alto riesgo de transmisión de la tuberculosis que actualmente se observa en esta isla obliga a introducir mejoras radicales y sostenidas en las medidas de control de esta enfermedad.
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