Retrospective active case finding in Cambodia: An innovative approach to leprosy control in a low-endemic country

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**ABSTRACT**

Currently, leprosy control relies on the clinical diagnosis of leprosy and the subsequent administration of multidrug therapy (MDT). However, many health workers are not familiar with the cardinal signs of leprosy, particularly in low-endemic settings including Cambodia. In response, a new approach to early diagnosis was developed in the country, namely retrospective active case finding (RACF) through small mobile teams. In the frame of RACF, previously diagnosed leprosy patients are traced and their contacts screened through "drives". According to the available records, 984 of the 1,463 (67.3%) index patients diagnosed between 2001 and 2010 and registered in the national leprosy database were successfully traced in the period 2012–2015. Migration (8.4%), death (6.7%), operational issues (1.6%) and unidentified other issues (16.0%) were the main reasons for non-traceability. A total of 17,134 contacts of traced index patients (average: 2.2 household members and 15.2 neighbors) and another 7,469 contacts of the untraced index patients could be screened. Among them, 264 new leprosy patients were diagnosed. In the same period, 1,097 patients were diagnosed through the routine passive case detection system. No change was observed in the relation between the rate at which new patients were identified and the number of years since the diagnosis of the index patient. Similar to leprosy patients diagnosed through passive case detection, the leprosy patients detected through RACF were predominantly adult males. However, the fraction of PB leprosy patients was higher among the patients diagnosed through RACF, suggesting relatively earlier diagnosis.

It appears that RACF is a feasible option and effective in detecting new leprosy patients among contacts of previously registered patients. However, a well-maintained national leprosy database is essential for successful contact tracing. Hence, passive case detection in the frame of routine leprosy surveillance is a precondition for efficient RACF as the two systems are mutually enhancing. Together, the two approaches may offer an interesting option for countries with low numbers of leprosy patients but evidence of ongoing transmission. The impact on leprosy transmission could be further increased by the administration of single dose rifampicin as post-exposure prophylaxis to eligible contacts.

1. Introduction

To date, no biomedical tests are available to easily and reliably diagnose subclinical *Mycobacterium leprae* infections and leprosy disease (Roset Bahmanyar et al., 2016). Likewise, efficacious vaccines specifically targeting *M. leprae* remain elusive (Steinmann et al., 2017). As a consequence, leprosy control largely depends on the recognition of the cardinal signs of leprosy disease by a health worker, followed by administration of multidrug therapy (MDT) (Smith et al., 2017). Early diagnosis is important for two main reasons: to reduce the risk that the patient develops irreversible disability, and to shorten the time the patient can contribute to the transmission of the infection (Smith et al., 2014; Smith and Aerts, 2014, 2015). As a relatively rare disease with initially inconspicuous and painless symptoms that can easily be mistaken for other dermatological conditions, health workers often lack experience to recognize the cardinal signs of leprosy. Further, patients...
tend to overlook symptoms and do not seek medical attention at an early stage. Consequently, leprosy is often ignored or diagnosed late, and a considerable proportion of newly detected leprosy patients suffer from severe morbidity (Anonymous, 2015).

To shorten the delay between the onset of leprosy disease and diagnosis, contribute to the training of the health workforce, and raise awareness among the public; mass campaigns and targeted group screenings are conducted in many leprosy-endemic countries (Schreuder et al., 2002). Typically, such activities focus on high-incidence communities, but they can also have more general reach. Further, they usually focus on the contacts of newly diagnosed leprosy patients since prolonged contact with an untreated leprosy patient is one of the key risk factors for developing leprosy disease (Moet et al., 2004; Moet et al., 2006). Contacts are usually categorized as household members, neighbors and social contacts such as class mates and co-workers. Close contact for more than 20 h per week and over several weeks has been recognized as the main threshold for increased risk of leprosy disease among contacts (Smith and Aerts, 2014). The contact definition applied in a specific programme depends on the local level of stigma, resources and operational feasibility.

In 1998, Cambodia reached the WHO-defined threshold of leprosy elimination, namely < 1 case per 10,000 population (CENAT – National Center for Tuberculosis and Leprosy, 2005). Unfortunately, this achievement has resulted in a diversion of attention to other public health issues. Human and material resources dedicated to leprosy control have consequently diminished, along with public interest in the disease and internal and external financial support to leprosy control. However, over one hundred new leprosy patients continue to be diagnosed in the country every year through passive case detection (2016: n = 154 (Anonymous, 2017)), and there is evidence for both, ongoing transmission (i.e. pediatric patients) and considerable delay until diagnosis (i.e. grade II disability) (Anonymous, 2015). Contrary to other countries, in Cambodia the contacts of newly diagnosed leprosy patients are not routinely traced and screened for signs of leprosy. In response, a unique approach to leprosy control has been developed in Cambodia, building on the concept of retrospective active case finding (RACF) that had been developed in the frame of tuberculosis control (Morishita et al., 2016).

In this article, we summarize the Cambodian experience with RACF to amplify the efforts for leprosy control in the country. We report on the feasibility and effectiveness of RACF as compared to the routine activities and summarize first findings. Last, we discuss future perspectives and integration with other innovative approaches for leprosy control. A special focus is on the coverage achieved with this approach, the optimal time span from diagnosis of the index patient until contact tracing and screening, and on the characteristics of the leprosy patients diagnosed through RACF as compared to those diagnosed through routine program activities.

2. Materials and methods

2.1. RACF and its implementation in Cambodia

The RACF project was jointly developed by the Cambodian National Leprosy Elimination Programme (NLEP), the Campagne Internationale de L’Ordre de Malte contre la Lèpre (CIOMAL) and Novartis Foundation. An inclusive contact definition was used that covered all household members and neighbors living within a radius of about 200 m around an index patient diagnosed in the country between 2001 and the onset of the program in 2011. The national database of leprosy patients in the country provided the starting point to trace index patients. The list was completed based on local records since the national list apparently was incomplete and address details for the index patients were sometimes missing. The tracing of the index patient and the screening of their contacts for signs of leprosy disease was then implemented by a mobile team in the frame of “drives” that systematically covered all 78 operational districts (OD) of the country until all ODs had been visited at least once; a goal achieved in 2015. The scheduling of the drives took the rainy season (ca. July-October) into account as periodic flooding compromises access to some areas. The mobile team included experienced leprologists from NLEP and CIOMAL, province- and district-level leprosy control staff, and local health care personnel. In parallel, routine leprosy control activities, namely passive case detection, continued throughout the country.

The final drive protocol was developed based on the experience gained through three initial drives during which the contacts of 1,818 index patients in 25 ODs had been screened and 277 new leprosy patients had been diagnosed. Similarly, the documentation of the drive activities evolved over time. Standardized documentation is available from drive 4 onwards.

In brief, field activities included a theatre play to raise awareness for leprosy in general and for the RACF mission in particular. The following day, index patients were visited and re-examined to confirm their leprosy status. Then, the household members of the index patient were screened for signs of leprosy disease, followed by the neighbors. Possible new leprosy patients identified through the screening process were examined by an experienced leprologist and diagnosis confirmed on the day of the drive. For newly detected patients, MDT was initiated immediately. Drive documentation focused on the newly diagnosed leprosy patients and on the household contacts for which individual demographic data were collected. From neighbor contacts without any signs of leprosy disease, only summary data were obtained (e.g. number of contacts screened).

2.2. Data analysis

Following the completion of the first phase of the RACF project, namely once all ODs had been visited at least once, all drive data were entered into a single database. Available data from the RACF drives included the general reports from the project build-up phase (drives 1–3) and detailed data from the fully operational phase (drives 4–11). However, as the procedures and reporting were designed, tested and continuously revised during the build-up phase of the RACF project, and no individual data were collected during the build-up phase, only data from drives 4–11 were considered in the current analysis. Also excluded from the more detailed analysis was both data on patients not initially included in the national leprosy database and data on their respective contacts. To compare the performance of RACF with routine activities, annual data from the national leprosy control programme were obtained from NLEP for the years 2001–2015. All data were stored in Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, United States of America); data management and analysis was done in Stata version 14 (Stata Corporation, College Station, Texas, United States of America).

Descriptive statistics was used to summarize key RACF and NLEP data with the aim to investigate the feasibility of RACF, describe the main characteristics of the index patients and newly detected leprosy patients among their contacts, and evaluate the effectiveness of RACF as compared to the routine activities in Cambodia. The feasibility of RACF was assessed through (i) the percentage of index patients that had been traced successfully; (ii) the number of household members and neighbors that were successfully screened, stratified by the presence or absence of the index patient on the screening day; (iii) the number of new leprosy patients detected among the contacts, stratified by household and neighbor contacts; and (iv) the fraction of new leprosy patients among contacts in relation to the number of years since the diagnosis of the index patient.

Standard demographic and leprosy-specific variables were used to characterize the index patients and newly detected leprosy patients among their contacts: sex (male/female), age group (<15 years and > 15 years of age), disability grade (DG) 0, I or II, and leprosy type (paucibacillary (PB)/multibacillary (MB)).
The effectiveness of RACF in Cambodia was described in terms of the total number of newly detected leprosy patients detected through passive case detection and RACF respectively. Particular attention is on shifts in the proportion of patients with MB or PB in the districts over the years and depending on the detection method.

3. Results

3.1. Feasibility of RACF—tracing of index patients and their contacts

Overall, 1,463 leprosy patients in 54 ODs who had been diagnosed between 2001 and 2010 and registered in the NLEP national leprosy database were identified as index patients for the RACF drives 4–11 (Fig. 1). These index patients belonged to 1,287 different households. Of the 1,463 index patients, 67.3% were successfully traced during the RACF drives 4–11 in the years 2012–2015. Reasons for non-retrieval of index patients were death (6.7%), migration (8.4%), operational issues (e.g. inaccessibility of an area; 1.6%), and unidentified other issues (16.0%). No clear trend in tracing rates over time could be observed. A total of 24,603 contacts of these index patients were screened: on average, 2.2 household members and 15.2 neighbors per traced index patient and 1.7 household members and 13.9 neighbors per missed index patient.

In 12 out of the 54 ODs (22.2%) covered by the drives 4–11 the index patient tracing rate was lower than 50%. In the three ODs (5.6%) where no index patients could be traced, a maximum of three index patients had been listed in the NLEP national leprosy database and identified for follow-up. In 29 ODs (53.7%), at least 70% of the index patients could be traced, including 15 ODs (27.8%) where at least 80% of the index patients were traced. Overall, no clear relationship became apparent between the number of index patients and the tracing rate. Similarly, no relationship between different reasons for reported non-traceability of index patients could be identified.

Table 1

<table>
<thead>
<tr>
<th>Screening outcome</th>
<th>Among contacts of 984 successfully traced index patients</th>
<th>Among contacts of 479 untraced index patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Household contacts</td>
<td>Neighbor contacts</td>
</tr>
<tr>
<td>Positive</td>
<td>63</td>
<td>29</td>
</tr>
<tr>
<td>Negative</td>
<td>2,105</td>
<td>14,828</td>
</tr>
<tr>
<td>Total</td>
<td>2,168</td>
<td>14,966</td>
</tr>
</tbody>
</table>

* New case detection rate per 1000 screened individuals.

The effectiveness of RACF in Cambodia was described in terms of the total number of newly detected leprosy patients detected through passive case detection and RACF respectively. Particular attention is on shifts in the proportion of patients with MB or PB in the districts over the years and depending on the detection method.

3. Results

3.2. Feasibility of RACF—diagnosis of leprosy patients

A total of 1,097 leprosy patients have been newly listed in the NLEP national leprosy database from 2012–2015. Over the same period, RACF identified 264 new leprosy patients. Specifically, through RACF a total of 201 new patients were diagnosed among the 17,134 household members and neighbors of the successfully traced index patients, which translates into a new case detection rate (NCDR) of 11.7 per 1,000 contacts screened (Table 1). Likewise, RACF identified 63 new leprosy patients among the 7,469 screened household members and neighbors of the index patients that could not be traced, a NCDR of 8.4 per 1,000 contacts screened. Overall, 75 new leprosy patients were identified among the 2,987 screened household members (NCDR household member screening = 25.1) and 189 were diagnosed among the 21,616 screened neighbors (NCDR neighbors screening = 8.7).

Index patients traced in the frame of the RACF project were diagnosed between 2001–2010, and new leprosy patients among their contacts were diagnosed between 2012–2015. Hence, there is a minimum of two years and a maximum of 14 years between the diagnosis of an index patient and the tracing and screening of contacts. A
comparison between the cumulative total number of new leprosy patients detected among contacts and the cumulative total number of underlying index patients in relation to the number of years that have passed since the diagnosis of the index patient shows an almost linear increase between three and 12 years post-diagnosis of the index patient (Fig. 2). Thus, new patients were found at similar rates among the contacts of index patients diagnosed between 3 and 12 years prior to the contact screening. The fraction of new leprosy patients among the contacts was slightly lower two to three years after the diagnosis of the index patient, as well as over 12 years after diagnosis.

3.3. Characteristics of leprosy patients diagnosed through routine services and RACF

No systematic difference was observed between the traced and the untraceable index patients in terms of their sex, age group, disability grade and leprosy type (Table 2). However, relevant data were missing for a large number of patients. The majority of the index patients that were appropriately documented in the NLEP national database were male, aged > 15 years and had MB leprosy with DGo. The completeness of the NLEP data was better for patients diagnosed in the years 2012–2015. If no systematic difference exists between the patients with complete data and the other patients, the key demographic and leprosy indicators of index patients diagnosed 2001–2010 and patients registered in the NLEP database in 2012 and 2015 appear to be comparable.

The leprosy patients detected through RACF among the contacts of index patients diagnosed between 2001 and 2010 were again predominantly male adults (Table 2). Of note, among household members the same number of male and female patients was detected while among neighbor contacts, male patients predominate. Very limited data is available on disability among the new patients detected through RACF, particularly among household members, when compared to the national cohort of passively detected new patients between 2001 and 2010 and between 2012 and 2015.

3.4. Leprosy patients who had been diagnosed but not formally registered in the national database

In the frame of the RACF activities, local Operational District registries were compared to the national leprosy database maintained by NLEP. As a result, a total of 270 leprosy patients were identified which had been diagnosed by local health services and received MDT but were never registered in the NLEP national leprosy database. Among them, 71 (26.3%) had been diagnosed before 2001, 36 (13.3%) had been diagnosed in 2001 or later, and for 163 (60.4%) no date of diagnosis is available. Generally, information on these patients is very incomplete, and no detailed analysis is possible to determine whether they are systematically different from the registered cohort. The drive teams made an effort to trace these patients and to screen their household members and neighbors. This resulted in the detection of an additional 13 and 27 new leprosy patients among their household and neighbor contacts, respectively. Both the 270 unlisted patients and the 40 new patients among their contacts are not included in the presented data, figures and tables due to the severe data incompleteness.

3.5. Effectiveness of RACF as compared to routine activities

In 34 of the 54 visited ODs (63.0%), the number of newly diagnosed leprosy patients was higher in the year of the drive compared to the year before and after. The increase in the number of new leprosy patients detected in the ODs in the year of a drive was more pronounced with regard to PB than MB patients, and was most clearly observed in 2012, 2013, and—to a somewhat lesser extent—2014 (Fig. 3). In 2015, neither an impact of the drive on the total number of patients detected nor on the proportion of patients with MB vs. PB leprosy can be observed. The relatively high number of new leprosy patients diagnosed in ODs visited in 2012 and 2013 compared to the later years can be explained by an initial focus of the drives on ODs with a high number of index patients diagnosed in the baseline period 2001–2010. The high baseline number would translate into a high number of contacts to be screened and apparently also a high number of new leprosy patients in the following period. No statement is possible at this point in time on the longer-term impact of drives on the number of leprosy patients detected in an OD since systematically collected follow-up data are not yet available.

4. Discussion

The intention of this article is to widen the current discussions about the most effective combination of approaches to identify leprosy patients and thereby contribute to the interruption of transmission (Bratschi et al., 2015). Cambodia is in a similar situation as many other leprosy-endemic countries that have reached a relatively low NCDR of
Table 2
Demographic and leprosy-specific characteristics of new leprosy patients detected through passive case detection and retrospective active case finding (RACF) in Cambodia, 2001–2015.

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Numbers and percentages of new leprosy patients</th>
<th>New patients detected through RACF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>481 (48.9)</td>
<td>271 (66.1)</td>
</tr>
<tr>
<td>Female</td>
<td>310 (31.5)</td>
<td>139 (36.9)</td>
</tr>
<tr>
<td>NA</td>
<td>193 (19.6)</td>
<td>69 (14.0)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child (≤ 15 years)</td>
<td>32 (3.2)</td>
<td>18 (9.4)</td>
</tr>
<tr>
<td>Adult (&gt; 15 years)</td>
<td>664 (67.5)</td>
<td>188 (34.7)</td>
</tr>
<tr>
<td>NA</td>
<td>288 (29.3)</td>
<td>273 (53.0)</td>
</tr>
<tr>
<td>Disability grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disability</td>
<td>395 (40.1)</td>
<td>231 (56.6)</td>
</tr>
<tr>
<td>Disability grade I</td>
<td>93 (9.5)</td>
<td>39 (66.1)</td>
</tr>
<tr>
<td>Disability grade II</td>
<td>116 (11.8)</td>
<td>55 (39.2)</td>
</tr>
<tr>
<td>NA</td>
<td>380 (38.6)</td>
<td>154 (14.4)</td>
</tr>
<tr>
<td>Leprosy type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paucibacillary</td>
<td>235 (22.9)</td>
<td>120 (48.6)</td>
</tr>
<tr>
<td>Multibacillary</td>
<td>555 (56.4)</td>
<td>288 (51.4)</td>
</tr>
<tr>
<td>NA</td>
<td>194 (19.7)</td>
<td>71 (14.8)</td>
</tr>
</tbody>
</table>

NA: not available.

0.10 in 2016 (Anonymous, 2017) and now seek effective ways to ensure early diagnosis of new leprosy patients (Anonymous, 2016). A mobile team of experienced staff implementing RACF with the support from local healthcare workers offers a potential solution to multiple challenges common across low-endemic developing countries, including the diminishing expertise among peripheral health staff to recognize leprosy patients, the concentration of new leprosy patients among contacts of index patients, and the need to raise awareness for the disease (Smith et al., 2014). In response to these challenges, the highly structured RACF approach has been developed and applied in Cambodia. The here presented first evaluation of this approach indicates that it could be more effective than a decentralized system of contact tracing and screening and it certainly facilitates the monitoring and quality control of routine activities. Another strategy for active case finding, namely population screening campaigns, are only recommended in areas with a relatively high prevalence of leprosy (WHO, 2016). The experience with RACF in Cambodia over the last years clearly demonstrates that a RACF approach is feasible and contributes to early case detection as indicated by the higher proportion of patients with PB leprosy diagnosed during the drives compared to the respective proportion in the routine data. However, it is equally clear that leprosy control cannot be based on RACF with mobile teams alone since the tracing of index patients and screening of their contacts critically depends on a functioning passive case detection system, i.e. a basic capacity to diagnose leprosy must be maintained in the health system. Last but not least, proper documentation including a national leprosy database is essential. This is especially apparent in the relatively high number of diagnosed leprosy patients that were not listed in the national leprosy database, and the high proportion of missing data even for basic indicators such as sex of index patients. The drives offered an opportunity to update that database.

The following points are offered for consideration when interpreting the results of the RACF project in Cambodia. First, the project had a rolling start with procedures and documentation being developed and refined over time. Hence, no detailed information about the first three drives is available and the present analysis focuses on data from drives 4–11. Of note, these first three drives targeted ODs with a relatively high number of leprosy patients, and resulted in the diagnosis of 277 leprosy patients among their contacts while drives 4–11 resulted in the diagnosis of 264 new leprosy patients.

Second, an analysis of temporal trends within the RACF data must take into consideration that districts with relatively higher NCDRs and good accessibility were visited first. This non-random selection might be a main reason for the absence of any perceptible impact of RACF activities on the total number of newly detected leprosy patients in 2015 (Fig. 3) when the districts with lowest priority—i.e. those with lowest number of index patients and worst accessibility—were visited. In order to provide further insights into the effects of RACF on the leprosy epidemiology over time, the need for systematically collected follow-up data cannot be overemphasized.

Third, no precise information is available on the fraction of eligible contacts that have actually been traced and screened. The 1,463 index patients belonged to 1,287 different households in which an additional 2,987 household members were screened. Hence, on average, 3.5 individuals per household were documented. According to the 2013 Inter-censal Population Survey of the Kingdom of Cambodia, the average Cambodian household size was 4.6 individuals in 2013 (National Institute of Statistics, 2013). According to these numbers, the RACF drives 4–11 may have covered 70–80% of all household contacts, but missed 1–2 individuals in each index patient household. While not properly documented, the available evidence indicates that a lower fraction of the neighbor contacts have been successfully traced and screened. Thus, the coverage of the contacts with the highest risk of disease, namely household contacts, was better than that of contacts with a lower but in comparison to the general population still elevated risk (Table 1 and (Moet et al., 2006)). In order to properly estimate contact tracing rates among those most at risk and to better tailor RACF efforts (e.g. most efficient definition of “contacts”), it seems advisable to fully document activities also for neighbor contacts and to conduct contact network analyses. Reportedly, the acceptance of leprosy screening among contacts is high. While no detailed data have been published with regard to leprosy, stigma was not perceived to be an
issue in a home TB screening project in Cambodia (Lorent et al., 2015).

Fourth, the achievements of the passive case detection system and the RACF should not be compared competitively, but rather interpreted as mutually enhancing. Due to its dependence on index patient information, RACF should be most efficient in areas where a high proportion of local leprosy patients have been diagnosed and properly documented. However, in such areas the number of undiagnosed new leprosy patients still to be detected through RACF would be lower than in an area with weak capacity at the level of the local health system. On the other hand, a certain proportion of new patients diagnosed in the frame of RACF would most likely have been picked up by the passive case detection system later in the same year. Moreover, RACF also aims to influence the behavior of the local population. For instance, sensitization and encouragement to self-refer to a health center in case of a symptom suggestive of leprosy is an integral aspect of the drives. However, likewise, it is conceivable that a negative screening outcome provides a false sense of safety and distracts individuals from seeking care in time.

In the light of the continuing absence of routine contact tracing and screening of newly diagnosed leprosy patients in Cambodia, a second phase of the RACF project in Cambodia has been designed and became operational in late 2016. It focuses on 31 high-priority districts selected based on a relatively high NCDR and a comparatively high proportion of pediatric, MB and male leprosy patients. In the frame of the second phase, post-exposure prophylaxis (PEP) with single dose rifampicin (SDR) is offered to eligible contacts in the household of the index patient and its five most immediate neighbor households, which is in line with the general outline of the Leprosy Post-Exposure Prophylaxis (LPEP) programme (Barth-Jaeggi et al., 2016). The documentation of the second phase will also be aligned with the standards established for the LPEP programme, part of which Cambodia will thus become. Another focus of the second phase will be the contact tracing rate, which should be further increased to maximize the impact of the drives on the NCDR and leprosy transmission. Last, a rigorous surveillance protocol is being applied to further improve the quality of the field procedures and the completeness of the patient and project documentation.

5. Conclusion

The RACF approach with mobile teams was found to be feasible and effective in detecting new leprosy patients among the contacts of previously registered patients. The concentrated effort of a small team of trained leprosy specialists supported by local staff allowed the efficient tracing and screening of contacts without the need to establish a national system for contact tracing. However, basic capacity to diagnose leprosy must still be maintained in the health system to ensure the correct diagnosis of self-referred patients. Furthermore, a well-maintained national leprosy database is essential. The addition of SDR PEP could considerably increase the impact of RACF on transmission, and together the two approaches might offer an interesting option for countries with a relatively low number of new leprosy patients but evidence of ongoing transmission.

Conflicts of interest

Novartis Foundation provided technical input in the design phase of the approach including data collection, and funded the implementation of the drives and the data analysis. All co-authors are either staff of the Novartis Foundation or worked as paid consultants for the project described here. The funder had no role in the interpretation of findings or decision to publish this manuscript.

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