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ORIGINAL ARTICLE

Feasibility of immunochemical faecal occult blood testing for colorectal cancer screening in Bulgaria

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Summary

Purpose: *Colorectal carcinoma (CRC) is the second most common cancer in Europe. Screening guidelines recommend a range of screening options that include faecal occult blood tests (FOBTs). The efficacy of FOBT-based CRC screening is dependent on the participation rate, thus emphasizing the importance of the latter. This study aimed at analysing the feasibility of CRC screening with immunochemical FOBT (iFOBT).*

Methods: *A cross-sectional study of 600 asymptomatic persons at average risk, aged ≥45years from urban and rural municipalities was performed. An educational brochure, iFOBT kit with translated colored leaflet, informed consent form and questionnaire were administered to participants by 30 general practitioners. Faecal samples were analysed for occult blood using point-of-care rapid iFOBT (cut off 10 ng(GPs)Hb/ml) by the patients themselves at home. The questionnaire aimed to establish if they encountered difficulties in self-testing and self-analysing. Direct and indirect measures of test feasibility were used difficulties for reported study participation rate.*

Results: *The participation rate was 78.8% (473 participants). Patients > 65 years (x^2=70.8, P<0.001), those with lower education level (x^2=82.1, p<0.001), and patients living in villages (x^2=4.3, p<0.05) reported difficulties more frequently and they needed help for self-testing by iFOBT. Positive test was found in 8.5% of all participants. Of them 19 persons (48.7%) had haemorrhoids, 8 (20.0%) benign neoplasms, and 3 (7.5%) had CRC.*

Conclusions: *CRC screening study by means of iFOBT as a point-of-care test proved to be feasible, since a high participation rate was obtained.*

Key words: *average-risk persons, colorectal cancer, general practitioner, immunochemical occult blood test, screening*

Introduction

According to recent statistical data CRC is the second most common cancer in Europe with the highest incidence in Slovakia, Hungary and Czech Republic [1]. Most recent screening guidelines, such as those by the United States Preventive Services Task Force, recommend a list of screening options that include FOBT [2,3]. Successful screening programmes for CRC have been proposed by the European Commission, developed and implemented as instituted population-based FOBT approach [4-7].

Recently, iFOBTs have been shown to be more sensitive than classic guaiac testing (gFOBT). Also, since iFOBTs are specific for human haemoglobin,

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they do not require dietary restrictions, thus potentially improving screening acceptability. Using a higher cut-off point, iFOBT offers a gain in both sensitivity and specificity in comparison to gFOBT [8-10]. As expected, higher cut-off points decrease sensitivity and increase specificity. Generally, iFOBT testing is more sensitive for cancers than for benign neoplasms [11]. iFOBT sensitivity and specificity based on subsequent colonoscopy were 65.8% and 94.6% for cancer and 27.1% and 95.1% for advanced neoplasm, respectively [12].

The efficacy of screening strategy based on FOBT has been established in several randomized controlled trials (RCT), leading to significantly reduced CRC mortality rates. The efficacy of FOBT-based CRC screening is dependent on the participation rate, thus emphasizing the importance of the latter [6,13-15].

Participation rate depends on the willingness of an individual to undergo a certain screening and may be influenced by perceived advantages and drawbacks of CRC screening test, knowledge and awareness of CRC [16]. The awareness of CRC is low in Europe, but people showed significant interest in taking up FOBT screening if offered free [17]. Low knowledge was associated with negative attitudes and both factors were related to low intentions to participate in CRC screening. Patients' preferences can have a major impact on their willingness to participate in screening campaigns for cancer [18-21].

A trend for increasing incidence in Bulgaria has been reported recently [22]. CRC incidence and mortality in Bulgaria ranked second in males and females among all cancers cases, after lung cancer in males and breast cancer in females, respectively. The estimated age-standardised rates of CRC incidence in Bulgaria for 2012 were 58 per 100,000 in males and 36 per 100,000 in females, being above the average rates for Europe (55,7 and 34,7, respectively [1].

The Bulgarian healthcare system is designed as a three-tier model, with GPs as gate keepers where screening for CRC with gFOBT as a preventive activity is paid by the National Health Insurance Fund. However, as of 2009, the opportunistic screening for CRC with gFOBT without centrally-organised programme and conducted with the assistance of GPs was discontinued due to poor compliance of the GPs and health-insured persons. Unlike other countries, where iFOBT is part of population-based screening programs, no systematic screening for CRC is performed in our country. Given the relatively low participation rates of screening in other countries it was interesting to clarity whether Bulgarian people would be willing to participate in the study for CRC screening using iFOBT. Our previous study revealed that Bulgarian health-insured people have a positive mindset and attitude and are willing to participate in cancer screening programmes by iFOBT at home [23].

The aim of this study was to investigate the feasibility of testing with the immunochemical faecal occult blood test as a CRC screening tool.

Methods

Study design

We performed a cross-sectional study to explore the feasibility of iFOBT as a part of the EGPRN project "Study of health-insured individual's compliance in CRC screening using iFOB test" (Project no. HP/2013.011 using iFOBT in the second largest district in Bulgaria – Plovdiv, initiated in April 2013). The survey took place in the period of June to September 2013 in the GP practices of one rural and one urban municipality.

Ethics

The study was approved by the Ethics Committee of the Medical University of Plovdiv (Protocol no.2/28.03.2013) and written informed consent was obtained from all participants. The study was supervised by the EGPRN Research Strategy Committee.

Study population

The expected minimum sample size calculations were based on the results from a previous study [23]. Given an expected proportion of 70% in one of the studied variables "awareness of the efficacy of the iFOB test" for a 95% CI with 5% precision, we needed at least 323 health-insured individuals in the analysis [24]. Since the expected non-response rate in questionnaire surveys in Bulgaria is very high, considering the probable percentage of failure or drop-out, the minimum number to recruit was increased to 600 persons.

The criteria of inclusion were: health-insured, asymptomatic average-risk for CRC individuals aged ≥45 years who had had at least one consultation with a GP in the previous 12 months. The exclusion criteria were: high risk of CRC (i.e., personal or family history of CRC, Crohn's disease, ulcerative colitis, or hereditary nonpolyposis CRC) or colonoscopy within the last 5 years.

Thirty GPs were randomly selected using data from the National Health Insurance Fund web site (http://www.nhif.bg/web/guest/113). Each GP was asked to randomly select by lottery twenty patients from their lists (a total of n=600 health-insured individuals).

Participation included completion of iFOBT within the study period.

Faecal occult blood test and intervention

A qualitative immunochromatographic test iFOBT for the detection of human haemoglobin in human faeces self-testing was used. There was no any cross reaction with the haemoglobin. The test is produced according to WHO-GMP, ISO 9001 and ISO 13485 standards. The test recognises only human haemoglobin with high sensitivity using monoclonal and polyclonal antibodies reagents. The cut-off value for a positive test was set at 10 ng/ml of haemoglobin.

The study kit contained a sample collection test tube with dilution buffer, test cassette and colored instructions and illustrations for collection of faeces for performing and interpreting test results in Bulgarian and English.

No diet instructions were given and respondents were instructed to prevent contact of faeces with toilet bowl water. Instructions were given that the samples should not be collected during and following the 3 days of a menstrual period, or if the patient suffered from bleeding haemorrhoids or blood in the urine' contributing thus to a false-positive result.

The targeted population was contacted and invited by their GP, via call or e-mail to explain the aim and description of the study. Each GP was informed by the investigators in advance about the test patterns and its efficacy [23,25]. In the case of a contacted person who declined participation, another person from the GP list was contacted until the planned recruitment target was achieved. After obtaining an informed consent, each participant was provided with a free test kit, educational brochure and a questionnaire. If needed, additional information was provided by the GP during the visit. The educational brochure contained colored illustrations and concise information on CRC incidence and mortality, risk factors, target populations, benefits of screening, faeces sampling procedure, follow-up examination and instructions (the brochure was available upon request).

The participants were invited to use the kit for self-testing at home, following the instructions according to the international standards. They were asked to obtain one faecal sample at home for the iFOBT using a rod contained within the collection tube, to insert the rod with the collected samples into the test tube and to shake it after closing. Then, they had to draw 3 drops of sample into the hole of the test cassette and after 5 minutes to interpret the result.

After having carried out the self-testing, the participants completed the questionnaire and handed it out personally to their GP within the following two weeks. If no response was received from the participants at the end of this period, a reminder call by the GP or an e-mail message was sent for a reply in the subsequent two weeks. For a further follow-up of the participants, the GP registered the result on a check sheet for each patient and coded it by one and the same number, together with the completed questionnaire. In the case of positive or invalid results, the participants were invited to repeat the testing. The GP was responsible for referring patients with at least one positive test result to a gastroenterology or a surgery office for further evaluation by fibrocolonoscopy. After a period of a further two months for the results of the fibrocolonoscopy in the cases of positive test to arrive, the codded questionnaires and results were provided to the investigators (Figure 1).

Questionnaire and measures

We designed and created an original questionnaire as a survey tool and was tested in a pilot sample of patients. The administered questionnaire consisted of single-choice questions in several panels: difficulties in performing iFOBT; need for assistance in performing test; need for assistance in the interpretation of test results, need for more information and demographic characteristics as well as one open-ended question related to the description of difficulties with using the test. Ten of the respondents used the option for open-ended question and their replies were summarised in two main groups: difficulties with the technical procedure of carrying out iFOBT and difficulties with taking a stools sample.

Direct and indirect measures of test feasibility were used for reported difficulties and study participation rate. Participation rate was defined by the returned questionnaires after completion of the test.

Statistics

Data were presented as mean ± SD, 95% confidence interval (CI) or frequency (%), as appropriate. Descriptive statistics and frequency distribution analysis were used. Chi-square test was applied to test the associations between categorical variables and the independ-

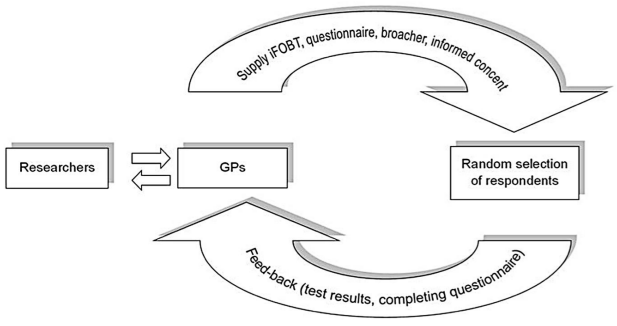

Figure 1. Schematic study presentation for CRC screening of participants using self-iFOBT.

ent-sample Mann-Whitney U test was used to compare continuous variables. A p value of <0.05 (two-tailed) was considered statistically significant. All data were elaborated and analysed using SPSS software, v.17. (SPSS Inc, Chicago, Ill).

Results

GP characteristics

Of all GPs 17 were urban and 24 were females. The mean number of patients per GP was 1522 (95% CI 1476.4-1568.8; range 600-3500), with a mean number of daily visits 27 (95% CI 26.9-27.7).

Patient characteristics

A total of 600 persons were invited to participate. The mean patient age was 61 ±10.29 years. Females were 382 (54.7%). Out of all participants, 260 (43.3%) lived in villages. About 12.3% (N=74) of the respondents had primary education, secondary education had 322 (53.7%) and tertiary education or above 204 (34.0%). There were no differences between participants and non-participants in relation with the demographic characteristics. The data for non-participants were obtained by using the software program of the National Association of General Practitioners in Bulgaria. The gender ratio from the two municipalities was: Maritsa (male:female=0.50:0.50); Plovdiv (0.47:0.53). According to the main socio-demographic characteristics, the study population in our sample was similar to the population of Bulgaria (data not shown).

The participation in the screening, iFOBT results and colonoscopy in positive cases is shown on the flow diagram (Figure 2).

Out of all 40 patients with positive test, 19 (47.5%) had haemorrhoids, 8 (20.0%) had benign neoplasms, 3 (7.5%) had CRC while 10 (25.0%) had no feedback from their further examination during the study period.

Participation rate and related factors

The overall participation rate was 78.8% with 473 participants. Demographic data, participation and completion test rates are presented in Table 1.

Participation was significantly lower in males (x^2=10.88, p=0.001), in the older (>65 years) age group (x^2=8.87, p=0.03) and persons living in villages (x^2=13.22, p=0.00). We found a statistically significant difference in the mean age between individuals who performed the test and those who did not (Mann-Whitney U test=25706.0, p=0.013). The proportion of participants who performed the test was highest (N=152, 85.9%) in the group aged 45-54 years and decreased down to 70.3% (N=45) with increased age of the participants (>75 years, x^2=10.16, p=0.001). The level of education did not have any influence on the participation in the CRC screening.

We also found a statistically significant difference in the mean daily workload between persons who performed the test and those who did not (Mann-Whitney U test=24521.0, p=0.001). The percentage of respondents who performed the test (participation rate) was significantly higher in ur-

Table 1. Patient characteristics of the iFOBT study

	*Completed iFOBT**		*Non completed iFOBT*		*Total*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Gender							
Male	198	72.8	74	27.2	272	100.0	0.001
Female	275	83.8	53	16.2	328	100.0	
Age, years							
45-54	152	85.9	25	14.1	177	100.0	0.03
55-64	128	77.1	38	22.9	166	100.0	
65-74	148	76.7	45	23.3	193	100.0	
≥75	45	70.3	19	29.7	64	100.0	
Place of living							
Urban	250	73.5	90	26.5	340	100.0	0.000
Villages	223	85.8	37	14.2	260	100.0	
Education							
Lower	305	77.0	91	23.0	396	100.0	0.782
Higher	168	82.4	36	17.6	204	100.0	

* All numbers (percents) were computed out of all respondents with valid answers (out of all 473 respondents)

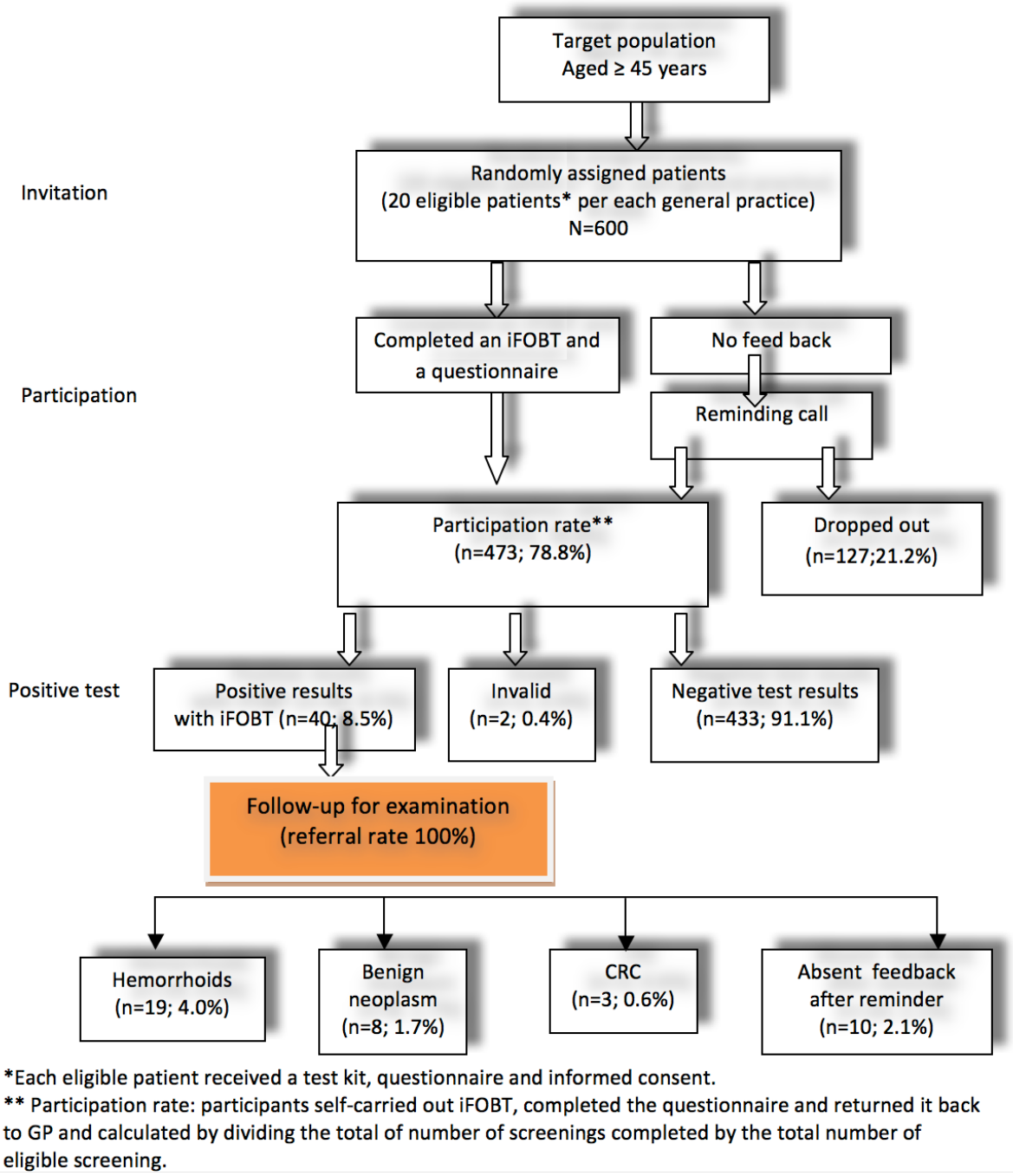

Figure 2. Flow chart of stages from invitation to final results of the study with numbers and percents.

ban practitioners (x^2=13.22, p=0.000), single practitioners (x^2=25.88, p=0.000), practitioners with lower daily workload (x^2=131.17, p=0.000) and those with smaller number of registered patients (x^2=65.77, p=0.000).

Feasibility of the iFOBT

The percent distribution of responses is presented in Table 2. It appeared that the gender was not related either to the need for help during the self-testing or to the detection of the result (p=0.104). Both urban and rural subgroups of the studied population had similar difficulties during the performance of the test while the persons from urban areas less frequently had difficulties in the detection and interpretation of the results (x^2=4.38, p=0.027).

Respondents with lower education encountered difficulties more frequently during the self-testing (x^2=81.40,p=0.000), self-evaluation (x^2=22.38, p=0.000) and they needed more assistance (x^2=27.36,

Table 2. Patients' views resulting for iFOBT experience

Answers *Feasibility of iFOBT according to patients*	*Yes* *N (%)*	*No* *N (%)*	*No answer* *N (%)*	*Total* *N (%)*
Did you meet difficulties during carrying out iFOBT?	15 (3.2)	448 (94.7)	10 (2.1)	473(100.0)
Did you need help in performing the test?	28 (5.9)	445 (94.1)	-	473(100.0)
Did you need help in interpretating of the test?	36 (7.6)	437 (92.4)	-	473(100.0)

p=0.007).

Higher level of difficulty was observed among the respondents aged >70 years (Mann-Whitney U test=12.3, p<0.001). In particular, out of the 10 participants who responded to the open question '*What types of difficulties did you encounter during self-test?*', 5 answered 'difficulty with breaking the top of the collection tube' and 5 mentioned 'difficulty with taking stools sample'.

In responding the question '*If you needed any additional information during self-test, who did you ask?*', about 90% (N=426) of the participants were satisfied with the information they were offered by their GP (brochure, information leaflet inside the test). Only 55 (9%) participants stated that they used additional personal discussion with GP or nurse on how to use the test kit.

Discussion

The response rate in our study was relatively high (78.8%). Good compliance (a participation rate over 50%) was noticed in 90% (N=27) of the GPs.

It is known that attendance is an important determinant of the efficacy of CRC screening though participation rates vary widely in different countries (17-61%) [7,26,27]. A compliance rate over 50% has been obtained in major clinical trials of CRC screening [14]. Therefore, we had estimated that a response rate >50% would be a realistic goal in each GP.

Participation rates are generally considered insufficient when compared to European guidelines for quality assurance in CRC screening that set a 45% as a minimum and advised a desirable rate of at least 65% [6]. In many countries, the yield of CRC screening has also remained suboptimal [15,28-30]. The participation rate for the population-based trial screening programme for CRC using iFOBT in Flanders was 44.3% which was discussed as acceptable according to Flemish standards [20]. However uptake of CRC screening in a pilot screening programme in the Netherlands has remained lower than the yield of breast and cervical cancer screening [31,32].

Factors affecting participation may be related to the populations or to the physicians [33].

The type of GP practising (single or group) and the place (rural or urban) of the GP influence the participation rate [16,17,26,27].

We also recognized that GPs in our study had a good knowledge about CRC screening using iFOBT and they delivered this information to the patients should they have been asked for.

Regardless of their specific role in the screening programme, GP involvement has been shown to improve patient participation [27]. The evidence for effectiveness strategies to increase cancer screening was based on several studies, and provided the basis for the Task Force recommendations for intervention use [34,35]. One of the last recommendations based on the increasing community demand for CRC screening with FOBT was expanded to include intervention using face-to-face education [36].

A substantial part of the participants (about 90%) in our study mentioned they did not need additional information about the iFOBT procedure. These results are similar to the results reported in the study by Van Hal Guido et al. where most of the respondents (80%) had declared that they were satisfied with the provided information and less than 10% wished to receive more information from their GP on how to obtain the stool sample [20].

It was shown that the public knowledge about risk factors and CRC screening of respondents from 21 European countries was insufficient and an educational programme should be essential to achieve high compliance in CRC screening [17]. The study by McCaffery et al. has examined the relationship between knowledge, attitudes to cancer and intentions to engage in CRC screening [18]. Contrariwise, increasing knowledge may re-

duce negative public perceptions of cancer and it was associated with higher intentions to participate in CRC screening [18].

As shown in Figure 2, the test-positive rate in our study was 8.5% (N=40). The referral rate was 100.0%, but the follow-up of the test-positive patients was 75%. In other studies, the FOBT positive rates varied from 2.6 to 5.6% (for 249 participants who performed the test) and compliance to colonoscopy ranged from 80.9 to 96.3% [14,29]. A randomized study comparing gFOBT and iFOBT reported a positive result in 5.5% of the participants using iFOBT and a compliance rate to colonoscopy of 83% [30].

We calculated a detection rate for CRC of 0.6% (out of all 473 participants), but in other studies this figure was 0.2% and 1.6% [14,30]. Howerver, in symptomatic patients the detection rate for CRC was 8.5% [37].

Strengths and limitations of the study

To the best of our knowledge, this is the first study in Bulgaria on CRC screening using iFOBT by patient self-testing. There are no other similar studies evaluating the feasibility of iFOBT as a point-of-care testing tool where the patients perform self-testing and interpretations of the results. We would also like to underline that this study was based not only on the subjective assessment and knowledge of the target group, but it was also relied on the respondents' actual experience in performing the iFOBT. Of note, neither specific laboratory expertise nor any expenses were required from the participants to perform the self-testing.

Our project covered only one region of Bulgaria and may be possibly extended further to the whole country. However, one limitation was that the non-participants did not report an exact reason for their non-participation. Also, due to the lack of data from a national coverage by such a CRC screening programme or data for other oncological diseases such as cervical cancer, breast cancer or prostate cancer, no comparisons could have been made in this regard.

Conclusion

The study for CRC screening using an iFOBT as a point-of-care tool has shown to be feasible, since good compliance and high participation rate were obtained. We may underline that an extension of this project across the whole country may be recommended, as well as a comparison with similar projects from other countries.

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