Real-time monitoring of results during first year of Dutch colorectal cancer screening programme and optimization by altering faecal immunochemical test cut-off levels

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ABSTRACT

Background

After careful pilot studies and planning, the national screening programme for colorectal cancer (CRC), with biennial faecal immunochemical tests (FITs), was initiated in the Netherlands in 2014. A national information system for real-time monitoring was developed to allow for timely evaluation. Data were collected from the first year of this screening programme to determine the importance of planning and monitoring for optimal screening programme performance.

Methods

The national information system of the CRC screening programme kept track of the number of invitations sent in 2014, FIT kits returned, and colonoscopies performed. Age-adjusted rates of participation, the number of positive test results, and positive predictive values (PPVs) for advanced neoplasia were determined weekly, quarterly, and yearly.

Results

In 2014, there were 741,914 persons invited for FIT; of these, 529,056 (71.3%, 95%CI: 71.2-71.4%) participated. A few months into the programme, real-time monitoring showed that rates of participation and positive test results (10.6%, 95%CI: 10.5-10.8%) were higher than predicted and the PPV was lower (42.1%, 95%CI: 41.3-42.9%) than predicted based on pilot studies. To reduce the burden of unnecessary colonoscopies and alleviate colonoscopy capacity, the cut-off level for a positive FIT result was increased from 15 to 47 µg Hb/g faeces halfway through 2014. This adjustment decreased the percentage of positive test results to 6.7% (95%CI: 6.6-6.8%) and increased the PPV to 49.1% (95%CI: 48.3-49.9%). In total, the first year of the Dutch screening programme resulted in the detection of 2,483 cancers and 12,030 advanced adenomas.

Conclusions

Close monitoring of the implementation of the Dutch national CRC screening programme allowed for instant adjustment of the FIT cut-off levels to optimise programme performance.

INTRODUCTION

Colorectal cancer (CRC) is a major health problem.[1] Fortunately, CRC is very suitable for screening and many countries have started CRC screening in the past decade. Choices for screening modality and strategy differ. Worldwide, many countries have implemented faecal occult blood testing (FOBT), in particular by means of faecal immunochemical testing (FIT).[2-4] Various FIT-based initiatives arise based on the growing recognition that an optimal screening method depends on population preference and the availability of resources.[5-9]

In the Netherlands, the screening modality was determined after a period of careful piloting. These pilot studies and subsequent modelling showed that screening by FIT was most acceptable to the Dutch population with a participation rate of up to 60%-62% in the first round, compared to 47%-50% for guaiac-based FOBT (gFOBT), 32% for sigmoidoscopy, 22% for colonoscopy and 34% for computed tomography colonography (CTC). As a result, FIT outperformed the other screening modalities in the detection of CRC per 1000 invitees.[10-14] FIT further allowed for adjustment of the cut-off level enabling a desired balance between true and false positive test results and colonoscopy referral rates to meet colonoscopy resource.[11,15]

Based on these findings, the Dutch government decided to gradually implement a national population-based screening programme based on biennial FIT from age 55 to 75 years at a cut-off level of 15 µg Hb/g faeces. During a 2-year planning period, a national information system was developed for real-time monitoring. Implementation of screening programmes requires careful planning, real-time monitoring and adjustment if needed to achieve the intended impact. Unfortunately, there is limited experience and literature on this process, which is relevant from a clinical as well as a public health perspective.

This article presents the outcomes of the first year of the Dutch CRC screening programme to illustrate the importance of planning and monitoring for optimal screening programme performance.

MATERIALS AND METHODS

The Dutch CRC screening programme

The Dutch CRC screening programme was implemented gradually by age group from 2014 onward, with a projected roll-out period of 5 years, allowing for timely increase of the colonoscopy capacity to ultimately accommodate the target population of 2.2 million invitees annually (Appendix I). The target population for 2014 consisted of all individuals reaching the age of 63, 65, 67, or 75 years in 2014. The oldest age group was included in 2014, because it was their only opportunity to be invited. The age groups around the median age of the programme were selected because these were expected to have the optimal

balance between CRC risk and remaining life-expectancy and experience the highest benefit from screening. Because the programme originally was supposed to start in 2013 and it had been publicly communicated that it would include screening for subjects born in 1938, these individuals also were invited despite having reached the age of 76 years in 2014. The target population received a pre-invitation letter by mail, followed 1 week later by an invitation letter by mail together with a single FIT test (FOB-Gold, Sentinel, Milan, Italy). After 42 days a reminder was sent automatically to nonresponders.

Each invitee was asked to perform a FIT and fill out a reply form including a sample date and return this in a prepaid envelope. Returning the FIT is considered informed consent, in accordance with the Dutch population screening act. The screening programme has been reviewed and approved by the Health Council as part of this act. Participants were informed about the FIT result by mail. If the FIT result equalled or exceeded the cut-off level, the family physician was informed and the participant was invited for a precolonoscopy intake interview in an accredited colonoscopy centre nearby. Participants whose sample was unreliable or not assessable were sent a new test. Individuals who actively deregistered from the programme were labelled as nonparticipants. Individuals who did not respond to the invitation were labelled as nonresponders.

Colonoscopy was the standard diagnostic follow-up test. All colonoscopies were performed by accredited endoscopists who perform at least 300 colonoscopies each year. All detected polyps were to be removed and sent for pathologic review.[16] In case of advanced adenoma (AA) or CRC, the participant was referred for further treatment and surveillance.[17]

Monitoring System

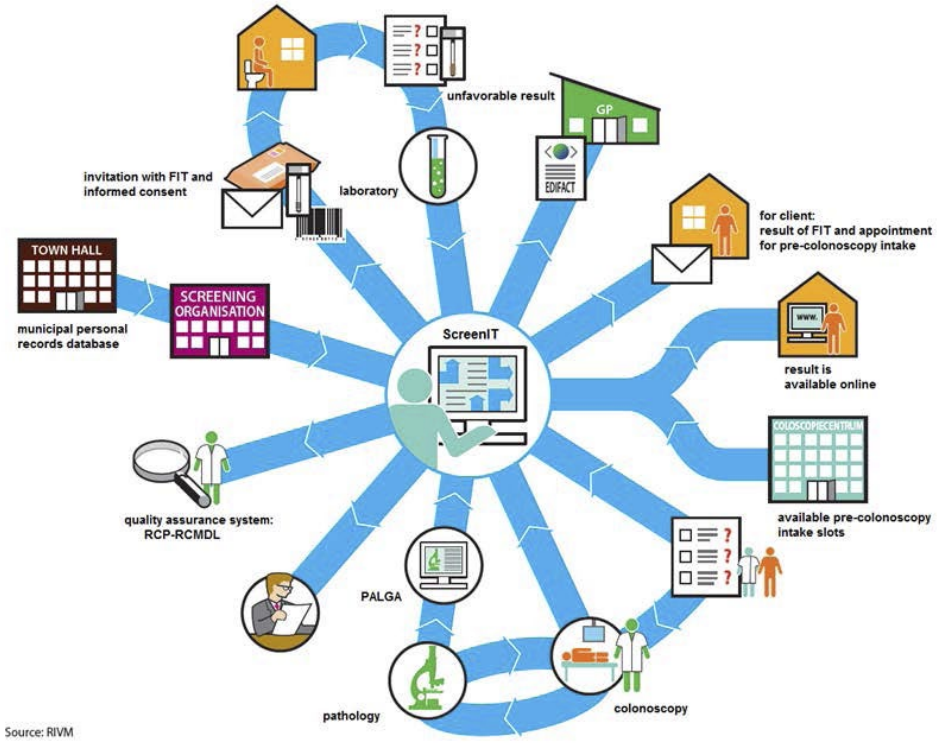
A national information system (ScreenIT, Topicus, Deventer, the Netherlands) was developed to structure the screening process automatically, continuously integrate information from different sources such as endoscopy units and pathology laboratories, and facilitate real-time monitoring (Figure 1). ScreenIT includes personal data from the municipal Personal Records database (personal details of every resident of the Netherlands), FIT results from the laboratories, available pre-colonoscopy intake slots, colonoscopy results from endoscopy centres, and pathology diagnoses from the Dutch national pathology registry (PALGA). Individuals had the right to object to data exchange for scientific research or quality assurance. Those who objected were labelled as nonresponders (n=24).

Screening outcomes from ScreenIT are reported weekly, quarterly, and yearly to the 5 regional screening organisations that are responsible for the execution of the programme.

Programme performance

By using the outcomes of the Dutch pilot studies with FIT (OC Sensor; Eiken Chemical, Tokyo, Japan) as a reference, the programme was designed to accommodate a 60% participation rate with FIT, with a positivity rate of 6.4% at a cut-off level of 15 µg Hb/g faeces. At this cut-

Figure 1: Graphical representation of the workflow in ScreenIT Information System*



Abbreviations: PALGA (pathology database), GP (general practitioner), MDL (gastroenterology), RCP-RCMDL (quality assurance system). Note: abbreviations are based on Dutch descriptions.

*The national information system ScreenIT automatically structures the screening process. It continuously integrates information from different sources, personal data from the municipal Personal Records database, like available pre-colonoscopy intake slots, pathology results from the national pathology registry PALGA, and endoscopy results.

off level the expected positive predictive value (PPV) for CRC and AA combined was 51.6%, and detection rates of CRC were 4.5‰ and of AA were 23.8‰.

Outcomes and Analyses

Data were collected to assess FIT participation rate, positivity rate, participation rate of precolonoscopy intake and diagnostic colonoscopy, PPV for advanced neoplasia, detection rate and false positive rate. Data on the invitees of 2014 were collected until March 31 2015. The FIT participation rate was defined as the number of individuals returning the stool sample divided by the number of individuals invited. The positivity rate was defined as the number of participants with a test result at or above the cut-off level divided by the number of participants with an assessable stool sample. The participation rate for precolonoscopy intake was defined as the number of participants who attended the pre-colonoscopy intake

divided by the number of persons with a positive FIT. The participation rate for colonoscopy was formulated as the number of persons who underwent a colonoscopy divided by the number of persons with a positive FIT. Advanced neoplasia (AN) was considered a relevant abnormality within a CRC screening programme.[18] AN was defined as CRC or any adenoma with histology showing 25% or greater villous component or high-grade dysplasia or adenoma with size 10 mm or larger. The PPV was calculated as the number of persons with AN divided by the number of persons who underwent a colonoscopy. The detection rate was defined as the proportion of individuals with AN detected during colonoscopy per 1,000 screened individuals with an assessable stool sample, also called the true positive rate. The false positive rate was defined as the number of persons without AN detected during colonoscopy divided by the number of screened persons with an assessable stool sample.

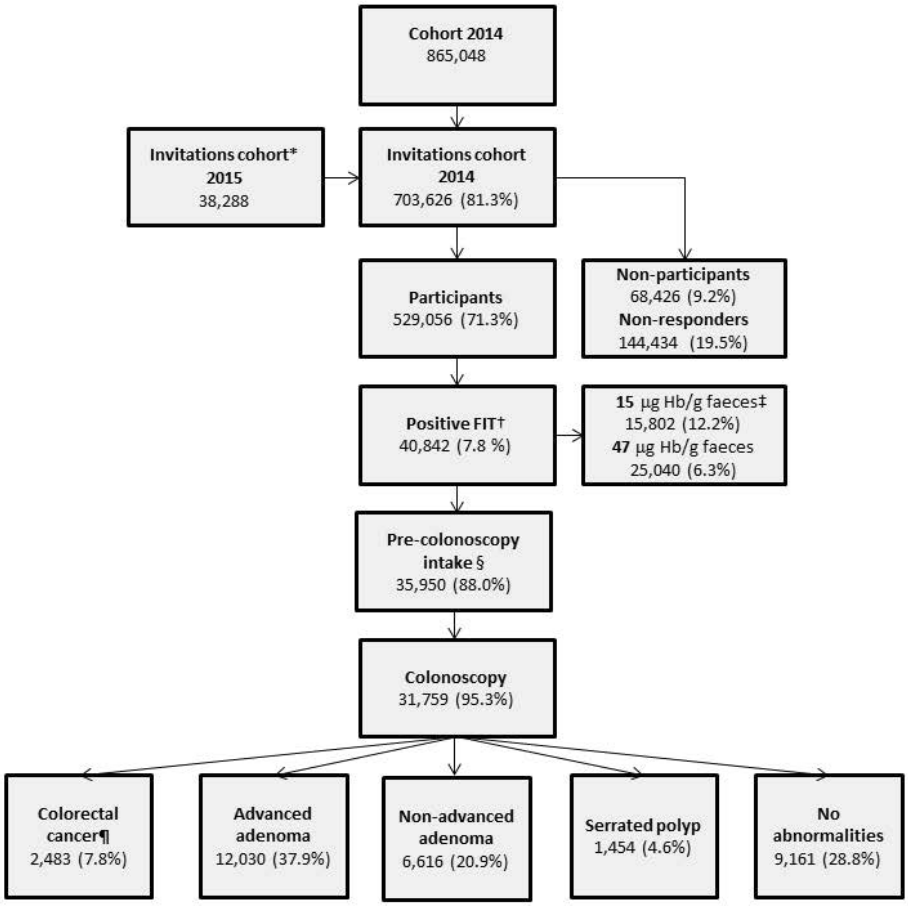
Proportions with 95% CIs were determined by descriptive analyses. Subgroup rates were age-adjusted to the age distribution of the total population invited calculated with a direct standardisation procedure.

RESULTS

Invitation and Participation

The target population for 2014 consisted of 865,048 persons. By the end of the year, 703,626 (81.3%) of those had been invited for screening. Weekly monitoring showed that in some screening regions the entire target population of 2014 had been invited before the end of the year. In these regions, an additional 38,288 persons aged 60 years were invited for screening, resulting in 741,914 invitees in total. Figure 2 shows the flow of individuals through the screening process. A total of 529,056 or 71.3% (95%CI: 71.2-71.4%) of the invitees returned the FIT to the laboratory. Of the 212,858 persons not returning a FIT, 32.1% were classified as nonparticipants and 67.9% were classified as nonresponders (including 24 who objected to data exchange). Of the 529,056 participants, 524,095 (99.1%) had an assessable FIT with consent form. Overall, the test result was positive for 40,842 individuals or 7.8% (95%CI: 7.7-7.9%) however these rates were different for the first half of the year compared with the second half year, as will be discussed in the next section. Of all individuals who tested positive, 35,950 (88.0%) had a precolonoscopy intake interview. In total, 33,313 (92.7%) individuals were advised to undergo colonoscopy. Colonoscopy and pathology data were available for 31,759 (95.3%) of the individuals who were recommended to undergo colonoscopy. Taken together, 77.8% of the participants with a positive FIT had undergone a colonoscopy. Excluding those for whom colonoscopy was not recommended (n=2,637), uptake of colonoscopy was 83.1%.

Figure 2: Flow of individuals through the screening process



Abbreviations: FIT (faecal immunochemical testing)

*As some screening areas had invited the entire target population already before the end of 2014, a number of individuals from the target population of 2015 were already invited in calendar year 2014.

† Including 24 individuals who objected to data exchange, who were also labelled as non-responders.

‡ Of all participants, 99.1% had an assessable FIT.

§ July 2014 the cut-off level for positivity was increased to 47 µg Hb/g faeces.

¶ Preceding the colonoscopy, a pre-colonoscopy intake interview takes places at an accredited screening colonoscopy centre. For 259 participants, no intake report was available in ScreenIT.

** Outcomes are based on the most advanced finding for each individual.

Positivity rate, PPV, and detection rate in the first half of 2014

During the first months of the programme, real-time monitoring detected an age-adjusted positivity rate of 10.6% (95%CI: 10.5-10.8%) at a cut-off level of 15 µg Hb/g faeces. At this cut-off level, the PPV for CRC and AA was 42.1% (95%CI: 41.3-42.9%) and detection rates of CRC and AA were 5.8‰ (95%CI: 5.5-6.1‰) and 30.8‰ (95%CI: 30.1-31.5‰), respectively

Table 1: Participation rates, positivity rates*, positive predictive values (PPVs) †and detection rates‡ for biennial FIT screening in the first year of the Dutch CRC screening programme

		Participation		Positivity		PPV CRC		PPV AA		Detection rates CRC		Detection rates AA	
	Cut-off	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	‰ (95%CI)	n	‰ (95%CI)
All	*Total*	529,056	*71.3 (71.2-71.3)*	40,842	7.8 (7.7-7.9)	2,483	7.8 (7.5-8.1)	12,030	37.9 (37.3-38.4)	2,483	4.7 (4.6-4.9)	12,030	23.0 (22.6-23.4)
Men		256,737	70.3 (70.1-70.4)	24,221	9.5 (9.4-9.6)	1,516	8.0 (7.6-8.4)	7,761	41.0 (40.3-41.7)	1,516	6.0 (5.7-6.3)	7,761	30.5 (29.9-31.2)
Women		272,319	72.3 (72.2-72.5)	16,621	6.2 (6.1-6.3)	967	7.5 (7.1-8.0)	4,269	33.3 (32.5-34.1)	967	3.6 (3.4-3.8)	4,269	15.8 (15.4-16.3)
60		26,622	69.5 (69.1-70.0)	1,310	5.0 (4.7-5.3)	38	4.3 (3.2-5.9)	332	37.8 (34.6-41.0)	38	1.5 (1.1-2.0)	332	12.7 (11.4-14.1)
63		89,420	74.2 (73.9-74.4)	4,842	5.5 (5.3-5.6)	273	7.3 (6.5-8.1)	1,475	39.2 (37.7-40.8)	273	3.1 (2.7-3.5)	1,475	16.7 (15.8-17.5)
65		116,998	74.3 (74.1-74.5)	7,906	6.8 (6.7-7.0)	421	6.7 (6.1-7.3)	2,503	39.6 (38.4-40.8)	421	3.6 (3.3-4.0)	2,503	21.6 (20.8-22.4)
67		141,682	74.5 (74.3-74.7)	9,593	6.8 (6.7-7.0)	633	8.2 (7.6-8.9)	3,110	40.4 (39.3-41.5)	633	4.5 (4.2-4.9)	3,110	22.1 (21.4-22.9)
75		79,095	67.1 (66.8-67.3)	7,789	9.9 (9.7-10.2)	538	9.2 (8.5-9.9)	2,188	37.3 (36.0-38.5)	538	6.9 (6.3-7.5)	2,188	28.0 (26.8-29.1)
76		75,239	64.1 (63.8-64.4)	9,402	126 (12.4-12.9)	580	8.0 (7.4-8.7)	2,422	33.5 (32.4-34.6)	580	7.8 (7.2-8.5)	2,422	32.6 (31.3-33.9)
All	*15 µg*	130,457		15,802	12.2 (12.0-12.4)	911	7.2 (6.8-7.7)	4,319	34.3 (33.4-35.1)	911	7.0 (6.6-7.5)	4,319	33.4 (32.4-34.4)
age-adjusted§				*15,802*	*10.6 (10.5-10.8)*	*911*	*6.8 (6.4-7.2)*	*4,319*	*35.3 (34.6-36.1)*	*911*	*5.8 (5.5-6.1)*	*4,319*	*30.8 (30.1-31.5)*
60		-		-	-	-		-		-	-	-	-
63		2,709		207	7.7 (6.7-8.8)	8	4.6 (2.3-8.9)	63	36.0 (29.2-43.4)	8	3.0 (1.5-5.9)	63	23.4 (18.3-29.8)
65		28,812		2,598	9.1 (8.8-9.4)	123	5.6 (4.7-6.6)	816	37.0 (35.0-39.0)	123	4.3 (3.6-5.10	816	28.5 (26.7-30.5)
67		16,726		1,753	10.5 (10.1-11.0)	102	7.0 (5.8-8.5)	534	36.9 (34.5-39.4)	102	6.1 (5.1-7.4)	534	32.1 (29.5-34.9)
75		26,446		3,454	13.2 (12.8-13.6)	217	8.0 (7.1-9.1)	938	34.8 (33.0-36.6)	217	8.3 (7.2-9.4)	938	35.8 (33.6-38.1)
76		55,764		7,790	14.1 (13.8-14.4)	461	7.6 (6.9-8.3)	1,968	32.3 (31.2-33.5)	461	8.4 (7.6-9.2)	1,968	35.7 (34.2-37.3)
All	*47 µg*	398,599		25,040	6.3 (6.3-6.4)	1,572	8.2 (7.8-8.6)	7,711	40.3 (39.6-41.0)	1,572	4.0 (3.8-4.2)	7,711	19.5 (19.1-20.0)
age-adjusted§				*23,730*	*6.7 (6.6-6.8)*	*1,534*	*8.9 (8.4-9.3)*	*7,379*	*40.2 (39.5-41.0)*	*1,534*	*4.4 (4.2-4.7)*	*7,379*	*20.6 (20.0-21.2)*
60		26,622		1,310	5.0 (4.7-5.3)	38	4.3 (3.2-5.9)	332	37.8 (34.6-41.0)	38	1.5 (1.1-2.0)	332	12.7 (11.4-14.1)
63		86,711		4,635	5.4 (5.2-5.5)	265	7.4 (6.6-8.3)	1,412	39.4 (37.8-41.0)	265	3.1 (2.7-3.5)	1,412	16.4 (15.6-17.3)
65		88,186		5,308	6.1 (5.9-6.2)	298	7.2 (6.5-8.0)	1,687	41.0 (39.5-42.5)	298	3.4 (3.1-3.8)	1,687	19.3 (18.4-20.3)

Table 1: Participation rates, positivity rates*, positive predictive values (PPVs) †and detection rates‡ for biennial FIT screening in the first year of the Dutch CRC screening programme (continued)

	Participation			Positivity		PPV CRC		PPV AA		Detection rates CRC		Detection rates AA	
	Cut-off	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	‰ (95%CI)	n	‰ (95%CI)
67		124,956		7,840	6.3 (6.2-6.5)	531	8.5 (7.8-9.2)	2,576	41.2 (40.0-42.4)	531	4.3 (3.9-4.7)	2,576	20.8 (20.0-21.6)
75		52,649		4,335	8.3 (8.1-8.6)	321	10.1 (9.1-11.2)	1,250	39.4 (37.7-41.1)	321	6.2 (5.5-6.9)	1,250	24.0 (22.7-25.4)
76		19,475		1,612	8.4 (8.0-8.8)	119	10.4 (8.7-12.3)	454	39.7 (36.9-42.5)	119	6.2 (5.2-7.4)	454	23.6 (21.6-25.9)

Abbreviations: FIT (faecal immunochemical testing), CRC (colorectal cancer), AA (advanced adenomas), PPV (positive predictive value)

* Positivity rate was defined as the number of participants with an unfavourable test result (above the cut-off level) divided by the number of participants with assessable stool sample. Numbers of participants with assessable stool sample are not shown in the table.

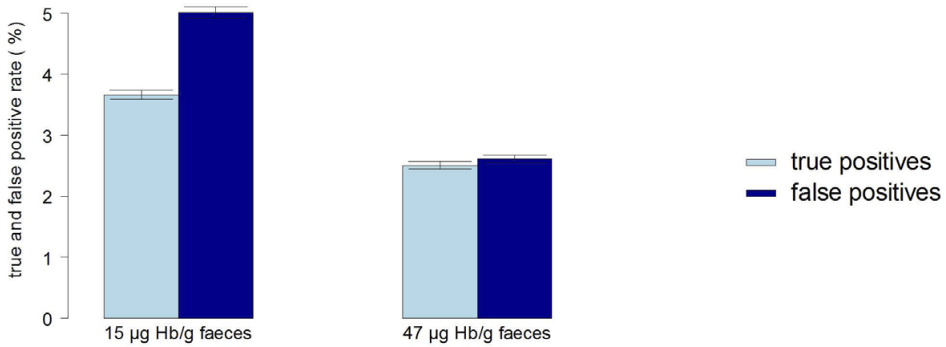
† PPV was calculated as the number of persons with CRC or AA divided by the number of persons who underwent colonoscopy. Numbers of positive individuals attending colonoscopy are not shown.

‡ Detection rate was defined as the proportion of persons with CRC or AA detected during colonoscopy per 1,000 screened persons with assessable stool sample. Numbers of participants with assessable stool sample are not shown.

§ The age-adjusted rates are calculated with the exclusion of the 60-year-olds screened in the second half of 2014 (with the cut-off level 47 µg Hb/g faeces).

(Table 1). Both positivity (10.6% vs 6.4%) and detection rates of CRC (5.8‰ vs 4.5‰) and AA (30.8‰ vs 23.8‰) in the first half of the year were higher than the expected programme performance. However, the PPV for CRC and AA was lower than expected (42.1% vs 51.6%), with relatively more individuals having a false positive result. The false-positive rate was 5.0% (95%CI: 4.9-5.1%), resulting in a higher burden of colonoscopy for both participating individuals and the programme. In addition, the participation rate also was higher than expected (71% vs 60%). Consequently, the demand for colonoscopies exceeded the capacity leading to a prolonged waiting period. There was no excess colonoscopy capacity in the Netherlands as a whole, so a further increase in colonoscopy capacity for the national programme was not possible in the short term. Because the programme was not performing according to the predefined quality indicators (i.e., positivity rate of 6.4; PPV of 51.6%; and follow-up colonoscopy within 3 weeks after a positive FIT), an immediate decision had to be made to improve the programme. A decision analysis was performed comparing 3 different methods to decrease colonoscopy demand in 2014: increase cut-off level, postpone screening in selected age groups, and forego screening in older age groups. This analysis showed that increasing the cut-off level not only resulted in the lowest decrease in CRC deaths prevented, but also resulted in a balance between harms and benefits of screening in accordance with the aims at programme start.[19] In consultation with all stakeholders, the Dutch National Institute for Public Health the Environment (RIVM) decided to increase the cut-off level because this was the most efficient way to optimise programme performance. Therefore, the cut-off level for referral for colonoscopy was increased to 47 µg Hb/g faeces in July 2014.

Figure 3: Comparison of the balance between true and false positives by the two cut-off levels



Abbreviations: FIT (faecal immunochemical testing), Hb (haemoglobin)

† True positive rate was defined as the number of persons with CRC or AA detected during colonoscopy divided by the number of screened persons with assessable stool sample.

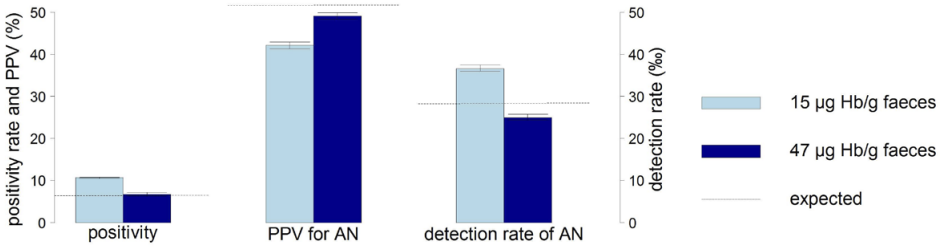
‡ True negative rate was defined as the number of persons without CRC or AA detected during colonoscopy divided by the number of screened persons with assessable stool sample.

§Rates are presented as age-adjusted rates, calculated with the exclusion of the 60-year-olds screened in the second half of 2014 (with the cut-off level 47 µg Hb/g faeces).

Positivity rate, PPV, and detection rate in the second half of 2014

The adjustment of the programme resulted in an age-adjusted positivity rate of 6.7% (95%CI: 6.6-6.8%) at a cut-off level of 47 µg Hb/g faeces. At this cut-off level the age-adjusted PPV for CRC and AA was 49.1% (95%CI: 48.3-49.9%). The age-adjusted detection rates at 47 µg Hb/g faeces of CRC and AA were 4.4‰ (95%CI: 4.2-4.7‰) and 20.6‰ (95%CI: 20.0-21.2‰), respectively. The false positive rate was 2.6% (95%CI: 2.6-2.7%). Increasing the cut-off level halfway through 2014 decreased the demand for colonoscopies by 37% and the number of false positive results by 48%, although CRC and AA detection rates decreased to a lesser extent by only 23% and 33%, respectively (Figure 3 and 4). If we would have applied a cut-off level of 47 µg Hb/g faeces during the first half year, 6433 (40.7%) fewer participants would have tested positive. This would have led to failure to detect 132 of 911 (14.5%) CRCs and 1351 of 4319 (31.3%) AAs (Appendix 2).

Figure 4: Comparison of age-adjusted† positivity rates‡, positive predictive value and detection rates§ by the two cut-off levels



Abbreviations: PPV (positive predictive value), AN (advanced neoplasia), Hb (haemoglobin)

* Comparing the two cut-off levels, the positivity rates, PPVs and detection rates were significantly different (p<0.05)

† All rates are presented as age-adjusted rates, with the exclusion of the 60-year-olds screened in the second half of 2014 (with the cut-off level 47 µg Hb/g faeces).

‡ Positivity rate was defined as the number of participants with an unfavourable test result (above the cut-off level) divided by the number of participants with assessable stool sample.

§ PPV was calculated as the number of persons with CRC or AA divided by the number of persons who underwent colonoscopy.

¶ Detection rate was defined as the proportion of persons with CRC or AA detected during colonoscopy per 1,000 screened persons with assessable stool sample.

DISCUSSION

These data show the additional value of real-time monitoring to successfully implement a national screening programme. A few months into the programme real-time monitoring showed a higher positivity rate and a lower PPV than expected. This resulted in a higher number of false positive test results, leading to unnecessary diagnostic colonoscopies with

associated risks. In July 2014, the programme was adjusted resulting in a lower positivity rate and fewer false positive results, which was more in line with expectations. Despite this adjustment, the entire target population of 2014 could not be invited within that calendar year owing to high participation and high referral rates for colonoscopy in the first half of the year, together leading to higher colonoscopy demand than capacity. As a whole, the first year of the national CRC screening programme resulted in a high number of participants and the detection of 2483 cancers and 12,030 advanced adenomas.

The participation rate exceeded the level of 65%, put forward as the desirable level of participation in the European Union guidelines for quality assurance in CRC screening.[18] It is remarkable that some countries with similar participation rates for population-based breast cancer screening programmes as the Netherlands, such as England and France, have lower participation rates for CRC screening.[20-22] Potential explanations for the high participation rate are the choice of screening modality, the efficient organisational structure of the programme (e.g., invitation-based, pre-invitation letter, and enclosing the FIT within the invitation set), a detailed information leaflet, and the fact that the FIT is free of charge.[23]

The higher-than-expected positivity rate in the first year can be explained by several factors. First, the age distribution of the first half of the year was skewed toward older ages, and older age is related to a higher positivity rate.[24] Second, the FIT (FOB-Gold) in the national programme was of a different brand than the FIT in the pilot studies (OC-Sensor). The choice of FIT in the programme was the result of a public tender required for all governmental purchases exceeding a certain monetary value. Previous studies have shown that FOB-Gold has higher positivity rates than OC-Sensor.[25,26] However, these studies did not standardise a cut-off value for a positive test result in µg Hb/g faeces, which was performed in the Dutch programme. Equal performance of both tests later was assessed in a confirmative trial.[27] Counterintuitively, positivity rates for both tests were higher in this fourth round of screening than in the third round, indicating a change in test performance between the 2 study rounds. The explanation may be that the manufacturers recently adapted the composition of the buffer fluid in the collection device to improve sample stability. Nevertheless, because selecting a new screening test is always subject to public tender, in the future we might first pilot a newly chosen test.

Participation in diagnostic colonoscopy was short of the minimally acceptable level of 85% and was lower than in the pilot studies and other FOBT-based screening programmes.[3,10,14,28,29] One explanation may be that not all colonoscopy results were integrated in ScreenIT because some individuals may have had a colonoscopy in centres outside the screening programme. Another potential explanation is that colonoscopy costs are considered standard medical care and therefore are covered by health care insurance. Because all Dutch citizens have a yearly obligatory deductible excess of 360 Euro participants who did not have previous medical costs in the calendar year were obliged to pay part of the colonoscopy costs. One last explanation might be that individuals refrained from colonoscopy or that colonoscopy was

not considered appropriate because of comorbidities. This also was reflected in the higher participation rate when excluding those for whom colonoscopy was not recommended. This may have had a relatively large impact because older age groups were disproportionally present in the 2014 target population.

The success of the Dutch CRC screening programme can in large part be attributed to its coordinated preparation and implementation, including piloting and monitoring. The piloting phase allowed for an evidence-based choice of the screening test, cut-off level, interval, and age range for the Dutch setting.[11-14] Real-time monitoring showed at an early stage that the programme performed differently than intended (e.g., higher positivity rate and a lower PPV) and therefore adjustments to the programme could be made immediately. Consequently, the programme now performs in line with expectations and recommendation of the Dutch Health Council.[3,11-14] The decision to adjust the cut-off level of the test was based on a thorough decision analysis, which has shown that the adjustment will lead to similar long-term effectiveness as the intended programme; close monitoring of programme performance should be continued for 2 reasons.[19] First, given the gradual implementation of the programme, the new cut-off level could be based on only a selected number of age groups. Second, results were all based on the first screening round. Data on participation rate, positivity rate, PPV, and the detection rate of subsequent rounds will be of interest to evaluate whether the chosen cut-off level will continue to provide the expected results. In the end, the interval cancer rate will be the most important performance parameter to monitor the adjustment of the programme.

One may argue that it is unethical to increase the cut-off level of a screening test after implementation of a screening programme, because an increase in the cut-off value would decrease detection of advanced neoplasia, and screening should not be implemented unless sufficient resources for follow-up evaluation and treatment have been secured.[30] However, in our opinion this consideration is not applicable to the Dutch programme. The increase of the cut-off value has not been made in the consideration of colonoscopy capacity (alone), but rather because the chosen cut-off value did not result in the intended balance of harms and benefits of the screening programme as recommended by the Dutch Health Council.[3] The adjustments of the cut-off value halfway through the year was necessary to ensure that the programme again met this intended performance.

Three limitations of monitoring the Dutch CRC screening programme are noteworthy. First, at this point in time, there is a delay of reliable information on the stage and localisation distribution of the detected CRCs and the occurrence of adverse events because not all data sources have been completely linked to ScreenIT. It is expected that this will occur within the next 1-2 years. Second, only colonoscopies performed in accredited colonoscopy centres within the programme are reported in ScreenIT. A national colonoscopy database will be set up in 2016 and potential linkage with that database will ensure complete catchment of all

colonoscopies by using the unique personal identifier. Finally, as already mentioned, current results concern only individuals age 60 years or older.

Notwithstanding these limitations, the design of the Dutch CRC screening programme may serve as a best practice for many screening initiatives currently being organised worldwide.[2] The implementation of the Dutch programme illustrates that even in evidence-based, well-planned programmes, programme performance can deviate from planning. Therefore, real-time monitoring systems are indispensable in ensuring quality in all aspects of screening programmes. A considerable amount of literature has been published on reports of organised screening programmes.[28,29] However, to our knowledge no other data on real-time short and long cycle monitoring of screening programmes is available. The results of the first year of the Dutch programme may serve as an example to show that real-time monitoring is different from a retrospective monitoring system. By using real-time monitoring, adjustments can be made instantaneously to obtain optimal programme performance and ensure a good balance between harms and benefits of the programme. The way monitoring is performed may differ throughout the world, to best fit specific conditions. But even in settings with opportunistic screening such as in the United States, monitoring systems can be put in place on local or institutional levels. The Kaiser Permanente Northern California organised CRC screening programme is an excellent example of setting up large organised programmes to document the entire screening process with the purpose of monitoring and quality assurance.[31]

At this phase of implementation, it was decided to stick to the original programme as much as possible and not experiment with alternative programme designs. Therefore, the cut-off level was increased the same way across the board, i.e. for all ages and screening rounds. It also was decided to stick to the re-screening interval of 2 years, even if the target population had not been completely invited yet. Once the programme has been fully implemented and established, future research should be performed to continually optimise the CRC screening programme. Looking at the impact of increasing the cut-off level, there are indications that the higher cut-off level has led to a greater reduction in screen-detected neoplasia in the older age groups compared with the younger age groups. Therefore, a differential cut-off level by age might lead to a more (cost-) effective screening programme. Decision analyses can be performed comparing such strategies to identify the optimal screening strategy for the current situation. Other examples of possible new strategies are applying different cut-off levels for the first and subsequent screening rounds or allocating different intervals based on the haemoglobin level of the previous screening round.

In conclusion, the Dutch national CRC screening programme was implemented successfully with high participation and yield. Real-time monitoring allowed for instant adjustment of the programme when it substantially differed from expected. Optimising the programme resulted in a programme that more closely meets expectations, with a better balance between true and false positive results.

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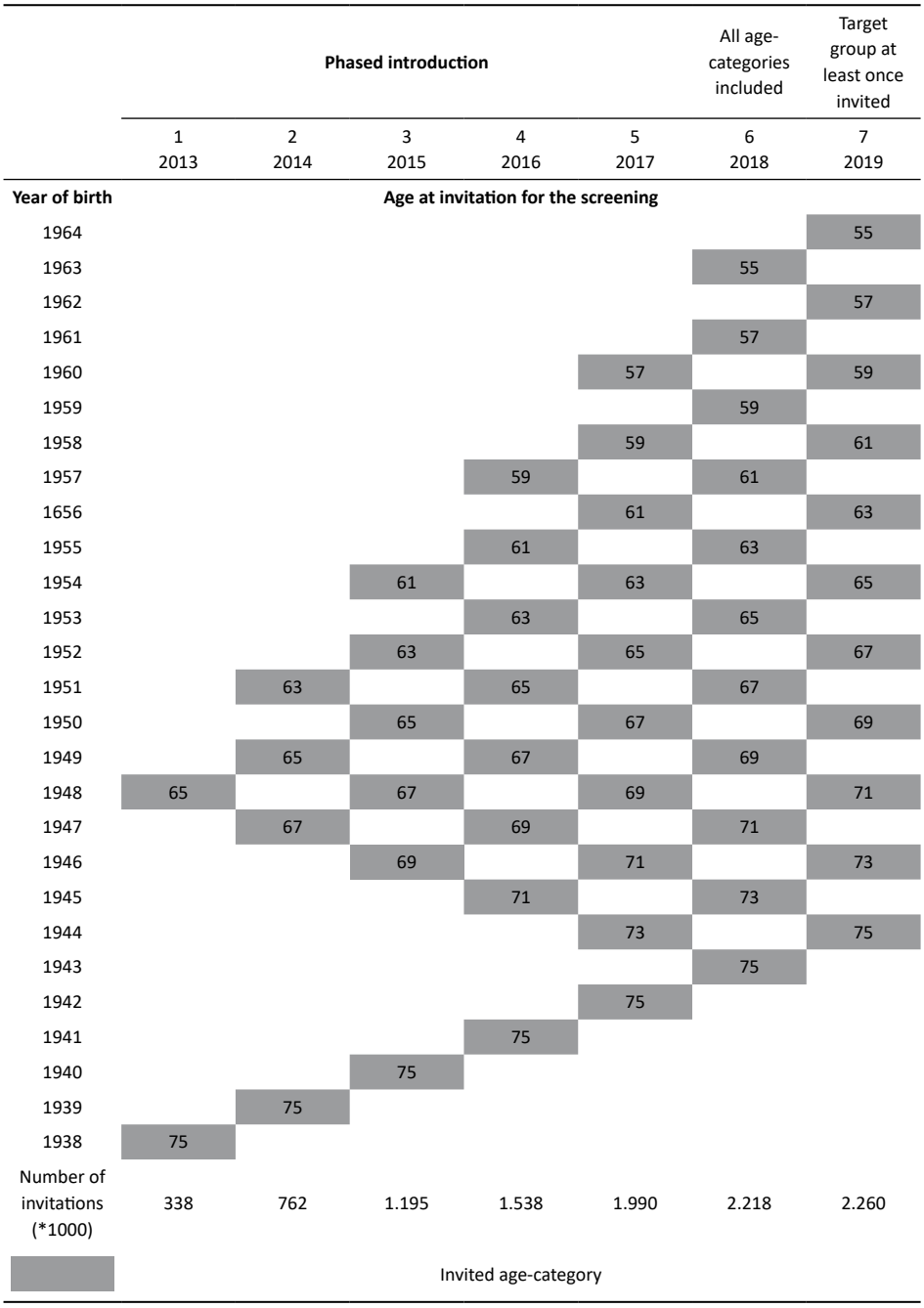
APPENDIX I

Figure 1: Original scenario for the gradual implementation of the Dutch national colorectal cancer screening programme



Original scenario for the gradual implementation by age groups to ultimately accommodate the target population of 2.2 million invitees (Source: RIVM).

APPENDIX II

Table 1: Calculated positivity rate* and positive predictive value (PPV) † for biennial FIT screening in the first year of the Dutch CRC screening programme at a cut-off level of 47 µg Hb/g faeces

		First half year 2014				Second half year 2014	
Cut-off level		*original 15 µg*		*15 µg ->47 µg*		*47 µg*	
	Positivity	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
All		15,802	12.2 (12.0-12.4)	9,369	7.2 (7.1-7.4)	25,040	6.3 (6.3-6.4)
age-adjusted§		*15,802*	*10.6 (10.5-10.8)*	*9,369*	*6.4 (6.3-6.4)*	*23,730*	*6.7 (6.6-6.8)*
60		-	-	-	-	1,310	5.0 (4.7-5.3)
63		207	7.7 (6.7-8.8)	125	4.6 (3.9-5.5)	4,635	5.4 (5.2-5.5)
65		2,598	9.1 (8.8-9.4)	1,533	5.4 (5.1-5.6)	5,308	6.1 (5.9-6.2)
67		1,753	10.5 (10.1-11.0)	1,056	6.3 (6.0-6.7)	7,840	6.3 (6.2-6.5)
75		3,454	13.2 (12.8-13.6)	2,066	7.9 (7.6-8.2)	4,335	8.3 (8.1-8.6)
76		7,790	14.1 (13.8-14.4)	4,589	8.3 (8.1-8.6)	1,612	8.4 (8.0-8.8)
	PPV CRC	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
All		911	7.2 (6.8-7.7)	779	10.4 (9.7-11.1)	1,572	8.2 (7.8-8.6)
age-adjusted§		*911*	*6.8 (6.4-7.2)*	*779*	*9.7 (9.2-10.2)*	*1,534*	*8.7 (8.3-9.2)*
60		-	-	-	-	38	4.3 (3.2-5.9)
63		8	4.6 (2.3-8.9)	8	7.3 (3.7-14.0)	265	7.4 (6.6-8.3)
65		123	5.6 (4.7-6.6)	109	8.3 (6.9-9.9)	298	7.2 (6.5-8.0)
67		102	7.0 (5.8-8.5)	87	10.0 (8.2-12.2)	531	8.5 (7.8-9.2)
75		217	8.0 (7.1-9.1)	183	11.3 (9.8-12.9)	321	10.1 (9.1-11.2)
76		461	7.6 (6.9-8.3)	392	10.9 (10.0-12.0)	119	10.4 (8.7-12.3)
	PPV AA	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
All		4,319	34.3 (33.4-35.1)	2,968	39.6 (38.5-40.7)	7,711	40.3 (39.6-41.0)
age-adjusted§		*4,319*	*35.3 (34.6-36.1)*	*2,968*	*40.9 (40.0-41.7)*	*7,379*	*40.3 (39.4-41.1)*
60		-	-	-	-	332	37.8 (34.6-41.0)
63		63	36.0 (29.2-43.4)	42	38.5 (29.9-48.0)	1,412	39.4 (37.8-41.0)
65		816	37.0 (35.0-39.0)	558	42.5 (39.8-45.2)	1,687	41.0 (39.5-42.5)
67		534	36.9 (34.5-39.4)	381	43.7 (40.5-47.1)	2,576	41.2 (40.0-42.4)
75		938	34.8 (33.0-36.6)	653	40.2 (37.8-42.6)	1,250	39.4 (37.7-41.1)
76		1,968	32.3 (31.2-33.5)	1,334	37.3 (35.7-38.8)	454	39.7 (36.9-42.5)

Abbreviations: FIT (faecal immunochemical testing), CRC (colorectal cancer), AA (advanced adenomas), PPV (positive predictive value)

* Positivity rate was defined as the number of participants with an unfavorable test result (above the cut-off level) divided by the number of participants with assessable stool sample. In this table, FITs was considered positive at a cut-off level of 47 µg Hb/g faeces.

† PPV was calculated as the number of persons with CRC or AA divided by the number of persons who underwent colonoscopy. Numbers of positive individuals attending colonoscopy are not shown.

§ The age-adjusted rates are calculated with the exclusion of the 60-year-olds screened in the second half of 2014.