Monitoring infectious diseases in blood donation processes selection of an optimal strategy

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Selection of an optimal strategy

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Abstract

The blood donation process is a delicate process. People voluntarily donate their blood which is used for different purposes. The donor is requested to go to a blood collection center and do a specific donation. Donors are divided in first time donors or repeat donors. The donor has restrictions on the blood donation, as there might be risk factors for the occurrence of a infectious disease. Beforehand the donor has to fill in a questionnaire to ensure the donation does not have that high risk to find an infection at the donor. The amount of repeat donors that tested positive for an infection has decreased over the last years. The current monitoring strategies might not be sufficient for the blood donation process and for that reason a more common used modeling method was used.

By simulating part of the process we were able to monitor in-control and out-of-control situations. By first modeling the process with two different models and by building a framework to make them comparable we could change the process to see differences in the strategies. By specifying realistic scenarios in which the process changed the current monitoring strategy was compared to the, for the process, new monitoring strategy. Out of the results the performance of the control charts, which are the visual tools to monitor the process, were determined to compare these charts. Based on the simulation results we can conclude that the new strategy can improve the current monitoring strategies of the blood donation process.

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I thank Sanquin for the tour I received in the headquarters in Amsterdam. It was interesting to see what is going on at the blood donation process. In my younger years my dad took me along as he was a blood donor but this way I also have a memory now for how important blood donors and blood donations are. From Sanquin in particular, I thank Ed Slot for allowing me to be part of this research for Sanquin and take a look in the blood donation database.

As for the other types of support I want to thank my parents, Jan and Ineke, my brother Polle and my sister Josje. These lines are probably not enough to show my gratitude on your time and patience and on many more levels.

I thank my fellow students along the way, with high probability I can state that you have not seen me study that hard for the last 9 months.

That one week of vacation I took in March was one of the best times I had abroad. Last but certainly not least, thanks to everyone from my athletics association and in particular fellow organizer Mark and everyone else on the training trip in Monte Gordo and Sevilla.

Contents

1. Introduction

1.1. Blood donation

Blood supply is very important in the public health care as blood is an essential part for life. The different components in blood, the blood cells, including red blood cells, leukocytes and thrombocytes, play a critical role in the treatment of an large amount of different life threatening diseases and (surgical) procedures. Blood is obtained in the Netherlands by blood donors who give blood voluntarily and do so for many years. The blood from the donors follows a process before it can be used for medicinal treatment, see Sanquin (2002). Since blood is vital for a persons life it can also be used to save lives. On average a person of 75 kilogram holds around 5.6 liter of blood and this blood is composed of blood cells (around 45%) suspended in blood plasma (55%). A donation from a donor of whole blood normally consists of 500 ml of blood and a donation of plasma consists of 500 ml blood plasma. When a donor gives a blood plasma donation, the blood cells are filtered and returned to the donor. This type of donation is less demanding for the donors body and therefore the donor is allowed to and able to donate blood plasma more often. The whole blood and blood plasma donations are the two most common types of donation. There are more types of donations like the donation of blood platelets or specific antibodies which are less often required.

Each person has a specific blood group, known as the ABO blood groups, which is genetically determined. As blood from different groups is needed, persons with specific blood groups are also needed as donors. Blood banks invite the donors and collect the blood. The invitations are determined by blood group, the type of donation and whether the donor has not been donating too much according to the specific restrictions. Blood banks are responsible for the recruiting, medical screening and blood collection from the donors. The persons that go to the blood bank are extensively screened before becoming a blood donor and be able to donate. A distinction is made before the donation into the group of first time donors, that are screened before becoming a donor and the group with repeat donors who after screening come to the blood/plasma collection centers (BCC) more often to donate whole blood or blood plasma.

The safety of the blood donation process is very important, both the safety of a donor giving the donation as the safety of the blood product given by a donor. The donor has to fill in a questionnaire and has a short blood check before a donation and, for the first time donor, an additional physical check is done. For the first time donor it is an extensive inquiry, to make sure that the health of the donor is not affected by a blood donation, when the donation is conducted the donor should be comfortable with it. Furthermore the donor's privacy is guaranteed as the donor will not know the receiver and the other way around.

A lot of administrative work is done by the blood bank as donors come to the collection centers for a specific donation. Besides storing all that information about the blood donation process also all the blood products are being processed and labeled. As the blood donations are separated and mixed it is important to follow and track all the steps that are done with each product. The inventory plays a big role as the blood products are stored until they are needed; this has as an advantage that donors have done another donation before the product is released from the inventory. The

inventory of the blood bank should always be able to deliver the amounts needed, especially in cases of emergencies.

All of the donors are screened and all blood donations are tested to check for the occurrence of infectious diseases. These are the safeguards to prevent the transmission of diseases. The blood and plasma donations have to be tested for infectious diseases which can occur. To identify the presence of viruses, serological and nucleic acid tests (NAT) are used. However, if a donor has an early stage infection, it may be missed as this specific infection has a window period, which is the time between the entry of an organism into the body until it becomes detectable by certain tests.

Three transmissible infectious diseases with severe health impacts that have been monitored for the past decades are Hepatitis-B Virus (HBV), Human Immunodeficiency Virus (HIV) and Hepatitis-C Virus (HCV). These viruses have different transmission pathways, through (organ) transplantation, non-sterile needles, sexual contact, pregnacy, vaginal delivery or breastfeeding. It is a known fact that one third of the world population is affected by Hepatitis-B Virus at one point in their lives, see the website of the World Health Organisation. The Hepatitis-B Virus is known to cause liver cancer. The Human Immunodeficiency Virus infects vital cells in the human immune system, which causes immunodeficiency, allowing other infections to occur more frequently and in greater severity. The Hepatitis-C Virus mainly persists in the liver and the virus is the leading cause for liver transplant. More information on this three infectious diseases is in Appendix A.

Considering the great health impacts, monitoring the presence of these viruses in donated blood is very important. The field that studies the behavior of (infectious) diseases is the study of epidemiology. Epidemiological studies focuses on patterns, causes and effects of the health and disease conditions in defined populations. Public health can generally benefit from such studies since epidemiologists provide policy decisions and give advice on the fields of medicines or methodologies in clinical research. Epidemiologists do this by collecting and analyzing statistical data and interpret different results to prevent the spread of diseases in the general population.

1.2. Problem description

Describing the problem will start off with some terminology widely used in the field of epidemiology. The incidence of a disease is the number of new infections of a disease expected within a specific time frame, the prevalence is the number of cases of an infection at a specific moment within the population. The incidence rate (IR), is given by the number of incidences in a specific time frame within a certain population, the period of one year and a population with a size of 100.000 is most commonly used, from the database on the website of medical terminology.

The Netherlands has a central database where the donor information is gathered, however the donors do not all go to the same place. There are multiple blood/plasma collection centers in the country for the donors to visit, normally located at strategic places like a hospital. Generally the incidence rate of a infectious disease can be determined by looking at the global (country) information, however since data of donations and infections for each donor center is available, this information gives more insight in the differences in incidence rates in different areas. Since there are over 300 blood collection centers in the Netherlands there are many different incidence rates. These different rates is one of the important topics concerning infectious diseases to guarantee the safety of medicines and blood products. The blood comes on a voluntary basis from donors and the incidence and prevalence of the diseases is determined by the incidences of these donors. There are risks in the blood donation process related to the infectious diseases and this is a highly sensitive topic. For

the incidence and prevalence rates, there are guidelines for the acceptable ranges. For all European countries infectious diseases within donor populations have to be calculated and reported annually, see EMA (2010). These reports are studied by epidemiologists and the authority to monitor effects, outliers and trends within the donor population that is part of the total population in a country. Based on the data, a model can be fitted to detect changes and evaluate the differences between centers.

Regulations can assure that there are thresholds for incidences and incidence rates at which an alarm can interact with parties that may or may not follow up on these alarms. Threshold settings can be determined in many ways, however the current criteria may have shortcomings. Testing for trends and outliers in both national as individual center level allow signaling with more know-how behind it. Situations with a significant increase in trends should be signaled in each country. This problem has been described in Janssen et al. (2009).

For the last years the incidence and prevalence of the infections within the donor population are decreasing and the incidences where an infection is found after testing the donor are stabilizing. Although this seems to be fine, the blood donation process might become very sensitive to changes in the stabilizing system. Therefore the following questions are to be answered in this report:

- Which model(s) can fit the incidence (rate) of particular infectious diseases (HBV, HIV and HCV) in the different blood collection centers?
- What are the differences in incidence in blood collection centers and donation or donor type?
- How can changes in the incidence rate best be determined?
- What is the optimal strategy to detect these changes?

In Chapter 2 an overview of the current methods is given and explained, in Chapter 3 an overview of the literature concerning the subject is provided and discussed. Chapter 4 describes the simulation, the input and the methods. In Chapter 5 all the choices and assumptions will be stated as we need a framework to compare the models used. The results from the simulation runs are described in Chapter 6. In Chapter 7 we obtain the conclusions and answer the research questions and in Chapter 8 we will offer recommendations for further research regarding the subject and on the guidelines for the EMA and Sanquin.

2. Current monitoring guidelines

The blood donation process has a long history and over the years the safety of the entire process became much more important. The unknown infectious disease HIV was able to be spread through blood transfusion in the early 1980's and overcome errors in the past with blood transfusion led to more regulations and changes to get rid of these problems. Blood banks were established to manage the blood business and so that a more systematic approach was guaranteed regarding the blood donations. The tests for the donated blood on infectious diseases have also been improved and new tests are being introduced to minimize undetected infections. The recruitment, selection and verification of donors is important such that specific risk factors of the donors could be identified beforehand. The infectious diseases have been continuously studied over the years so that much more is known about the nature of these diseases.

The detection of infectious diseases in the blood donation process has therefore developed over decades. The approach of counting the donors with infections is a to-the-point approach, which is explained in this chapter.

2.1. Methods of monitoring

Monitoring is very important in various applications, for example a patient in the intensive care needs heartbeat monitoring in order to alarm doctors in case of undesired changes. Monitoring information can give quick feedback on changes in a process. By monitoring processes better insights can lead to improvements. In the blood donation processes the occurrences of infectious diseased is monitored within the donor population. In this problem, analyzing the behavior of infections diseases within the donor population is done by monitoring the prevalence in first time donors (FTD) and the incidence rate of repeat donors (RD). The prevalence and incidence rate may have a certain behavior over time. This can be monitored to determine what is going on in the blood donation process regarding the infectious diseases within the donor population.

The first control chart, often named by its founder Walter A. Shewhart, is a chart to monitor process behavior, see Shewhart (1931, 1939). The control chart also provides a good overview of the incidence rates of infectious diseases over time, with warning and action limits. These limits are derived from the standard error of the sample mean, assuming that the number of infections found in the donor population X is distributed with a Poisson random variable. The mean and variance of the Poisson distribution with parameter λ are $\mu = \lambda$ and $\sigma^2 = \lambda$. Then the number of infections in a given year per donor is given by $\mu = \frac{X}{n}$, with n the size of the donor population. The standard error or standard deviation, σ_X, in a specific year is then given by (2.1), where μ_X is the sample mean of X and n is the size of the donor population.

$$\sigma_X = \sqrt{\frac{\mu_X}{n}} \tag{2.1}$$

The warning or alert limits can for example be set at a 2-standard error range and the action limits, the Upper Control Limit and Lower Control Limit, can be set at a 3-standard error range. See (2.2), where X is the sample statistic, μ_X is the sample mean of X, σ_X is the standard deviation of X and where L can be the desired distance from the average in standard deviations.

$$\begin{aligned} UCL &= \mu_X + L \cdot \sigma_X \\ Average &= \mu_X \\ LCL &= \mu_X - L \cdot \sigma_X \end{aligned} \tag{2.2}$$

The control limits have a different number of donations as a parameter, hence these limits take the yearly-changing number of donors into account. These limits included in the control charts gives a visualization of the incidence rate that is acceptable, the incidence rate that warns and the rate that requires certain actions. There are other possibilities and choices for the control limits. For example a sequential design based on the number of donors at a specific location.

2.2. Methods of testing

Several tests can be useful to monitor the incidence rate. For any test, one has to balance the sensitivity against the specificity. The sensitivity is the true positive rate (TPR), correctly rejecting the null hypothesis. The specificity is the false positive rate (FPR), rejecting the null hypothesis while the null hypothesis is true. These are better known as type I and type II errors. The type I error α is the significance and the type II error β. The receiver operating curve (ROC) gives a graphical plot of the TPR versus the FPR at various threshold settings. The curve can be used to select the desired significance α and power $1 - \beta$.

Detecting a change in the incidence rate can be tested by testing a proper hypothesis, for example stating that the incidence rate in a given year is the same as in the previous years versus an alternative hypothesis stating there is a change in incidence rate. To make it more mathematical, let X_1, X_2, ..., X_n be independent and identically distributed random variables with some distribution depending on a certain parameter $\theta \in \Theta$ with X the range of X_1, X_2, ..., X_n. With a partition of Θ into two disjoint sets Θ_0 and Θ_a the test becomes:

$$\mathrm{H}_0 : \theta \in \Theta_0 \text{ versus } \mathrm{H}_a : \theta \in \Theta_a \tag{2.3}$$

In (2.3), H_0 is the null hypothesis and H_a is the alternative hypothesis. The test finds, if possible, a subset with outcomes $R \subset \mathrm{X}$, known as the rejection region. With a critical value c and a test statistic T the one-sided region is given by $R = \{\, x : T(x) > c \,\}$. For testing there are many forms of hypotheses and choices for the test statistic and critical values. The p-value indicates the strength of evidence against H_0.

An example for a proper test statistic for testing the incidence rate is testing the likelihood ratio under the null hypothesis and the alternative hypothesis, as done in Janssen et al. (2009). The likelihood function is defined as $L(\theta) = \prod_{i=1}^{n} f(X_i; \theta)$, where X_1, X_2, ..., X_n is the observed realization of a sequence of independent and identically distributed (i.i.d.) random variables with

density function $f(x;\theta)$. The maximum likelihood estimator (MLE) is known as the value of θ that maximizes $L(\theta)$ and is denoted with a hat on the estimator, $\hat{\theta}$.

The log-likelihood is given as $l(\theta) = \log L(\theta)$. The likelihood ratio test statistic is then written as in (2.4) and the log-likelihood ratio test statistic is in (2.5).

$$T = \frac{\sup_{\theta\in\Theta_a} L(\theta)}{\sup_{\theta\in\Theta_0} L(\theta)} \tag{2.4}$$

$$T = \log\left(\frac{\sup_{\theta\in\Theta_a} L(\theta)}{\sup_{\theta\in\Theta_0} L(\theta)}\right) = \ell(\hat{\theta}_a) - \ell(\hat{\theta}_0) \tag{2.5}$$

Other notable testing strategies are calculating an exceedence probability based on the control limits which indicate whether an incidence rate is exceeding the action limits. Alarm levels can be calculated in different manners to set sequential thresholds depending on the specific donor population for an infectious disease. An easy way to do this is to simulate incidents depending on historical data on the incidence rate and set an desired alarm level based on a significance level. The alarm rate ratio (ARR) is the fraction of two incidence rates, that is the maximal acceptable incidence rate of the alarm level of a blood/plasma collection center divided by the average population of that BCC and the incidence rate of the global population.

2.3. Epidemiological data

In Kaleta et al. (2007), monitoring and testing is performed on the data of infectious diseases within the donor population in the Netherlands up to 2007. The number of blood collection centers for this donor population is divided in four regions. The data from 2008 up to 2012 are also freely available from the Sanquin, the Dutch blood bank, website. Also manufacturers of plasma medicines for the European market need to report infections in their donor population to the European Medicines Agency (EMA). The EMA collects epidemiological data on blood transmissible infections which is intended to obtain information on the infection risk in a specific donor population, see EMA (2010).

The EMA guideline proposes to take each incidence rate the rate of the previous three years as a reference. For each BCC and for the global incidence rate in the Netherlands the average rate, the LCL and the UCL can be calculated. For each infectious disease this leads to the following plots for HBV, HCV and HIV, see Figure 2.1. For these control limits we used the significance of $\alpha = 0.01$ and the *Šidák* procedure is performed on the data. The *Šidák* procedure, see Šidàk (1967), is a correction in the significance when performing multiple tests on the data.

In these control charts the top line (colored red) is the 3σ upper bound, the straight line (colored black) is the average rate for the global or regional donor population and the incidence rate is plotted. The 3σ lower bound (colored green) is most of the time equal to 0 and lies on the x-axis. The observed incidence rate is the moving line (colored blue) for the global donor population or the regional population. For each infectious disease the axes of the different populations have the same scale.

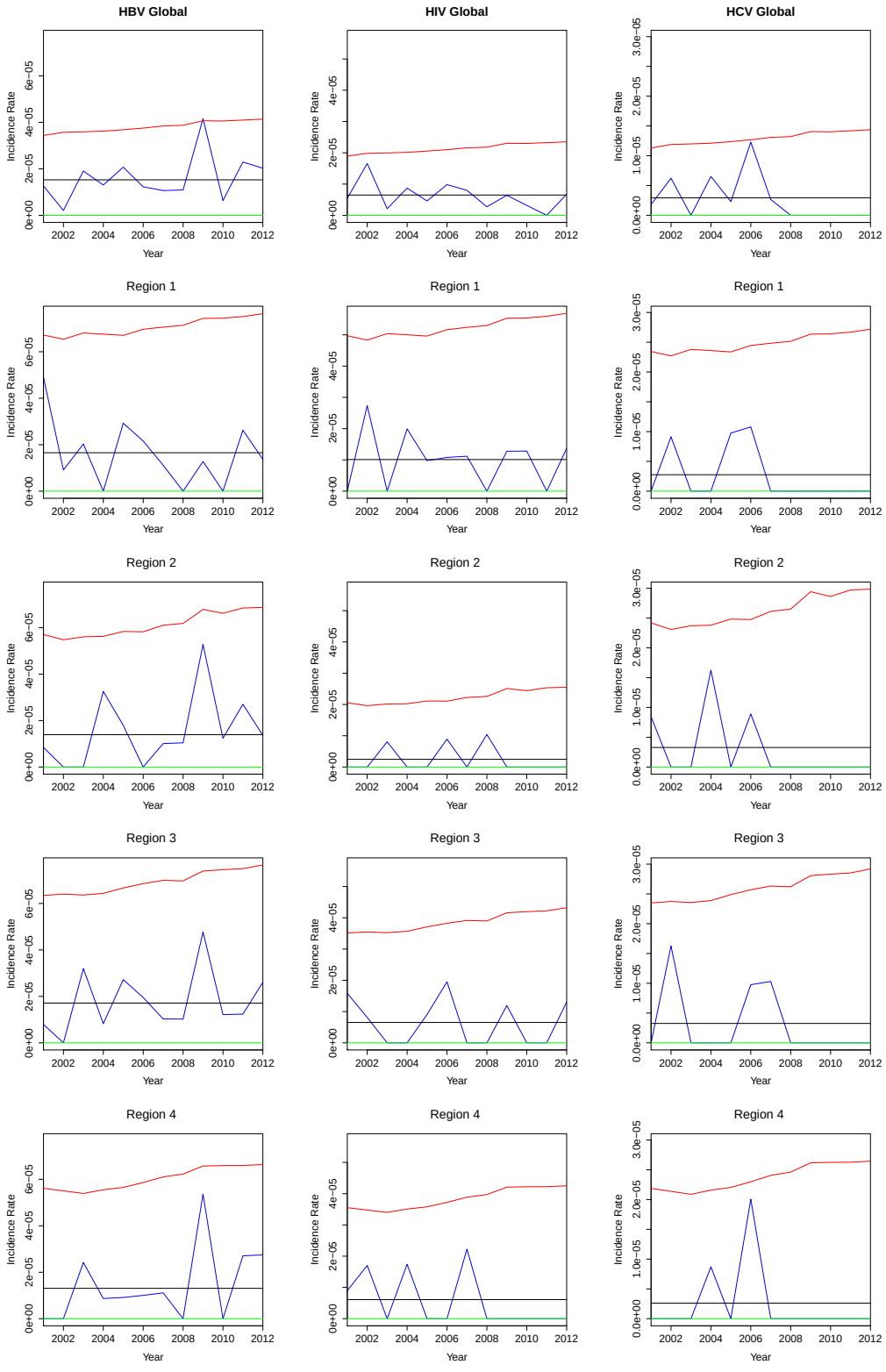

Figure 2.1.: Observed incidence rate (blue line), LCL (green line), UCL (red line) and the average incidence rate (black line) for HBV, HIV and HCV.

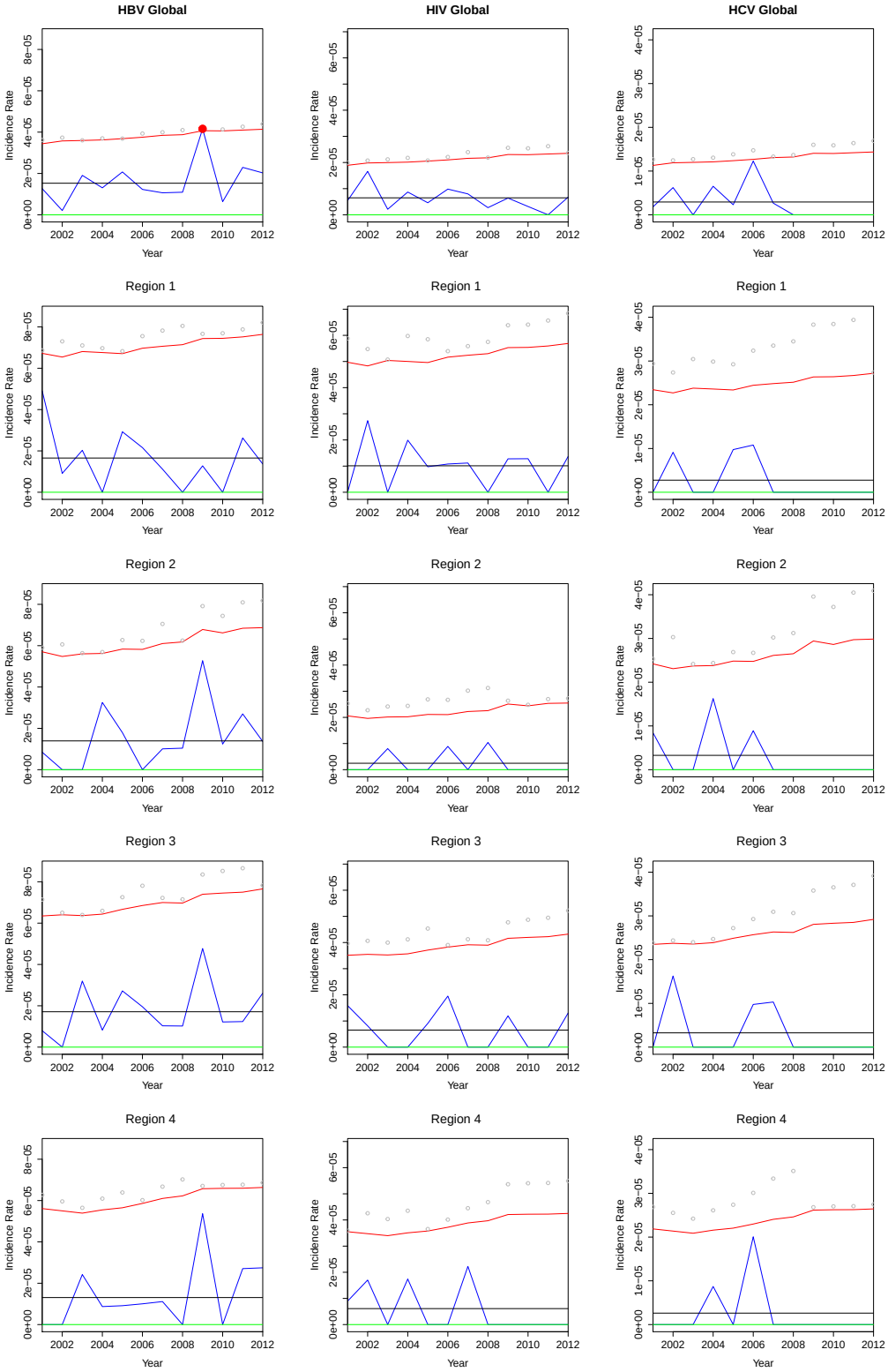

Figure 2.2.: Sequential Alarm Levels on UCL for HBV, HIV and HCV.

In Figure 2.2 we added the number of infections on the upper bound for the donor population in that year. As the observed incidence rate is related to the number of donors in each year there is also a number of infections that can be seen as the alarm level in that year. The alarm is indicated with a red dot, the open dots are the moving alarm levels. As the donor population over the years was decreasing, we can see the upper control limit move upwards. At some points the alarm level moves down as there are less infections found in the past years.

Besides these standard monitoring strategies, we have testing strategies specifically detecting trends and outliers. We can test a certain hypothesis for the incidence rate for each year. If we want to test the incidence rate for n years, say λ_1, λ_2, λ_3, ..., λ_n we can apply an appropriate hypothesis. For testing the incidence rate of the n'th year we have (2.6).

$$\mathrm{H}_0 : \lambda_1 = \lambda_2 = ... = \lambda_n \quad \text{versus } \mathrm{H}_a : \lambda_1 = \lambda_2 = ... = \lambda_{n-1} \neq \lambda_n \tag{2.6}$$

As in (2.5) we pick the log-likelihood ratio test statistic to verify the statement. The test statistic is as in (2.7) where N_j is the number of incidences and D_j is the number of donors for the years $j = 1, ..., n$.

$$T = \left(\sum_{j=1}^{n-1} N_j \cdot \left(\log \frac{\sum_{j=1}^{n-1} N_j}{\sum_{j=1}^{n-1} D_j} - \log \frac{\sum_{j=1}^{n} N_j}{\sum_{j=1}^{n} D_j} \right) \right) + N_n \cdot \left(\log \frac{N_n}{D_n} - \log \frac{\sum_{j=1}^{n} N_j}{\sum_{j=1}^{n} D_j} \right) \tag{2.7}$$

We use the Poisson distribution for the number of incidences with the incidence rate as parameter in a simulation. We test the test statistic of the observed data against the test statistic of incidences that gives the p-values for the tests, we do this by performing the simulation 1000 times. If we choose a maximal acceptable p-value of 0.05 we have to reject the null hypothesis for all test results in 2009 as in Table 2.4. The null hypothesis does not hold in 2003 and 2010 either if we make use of only one or two year(s) historical data. In that setting the test is more testing a difference of the incidence rates for those two years. This log-likelihood ratio test can be performed on all regional data and on all infectious diseases. The tables for the incidence rates of HIV and of HCV are in the Appendix Section A.2.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	0.0590	**0.0087**	0.4816	0.4089	0.3522	0.8279	0.9315	**0.0128**	**0.0028**	0.0870	0.8566
Two previous years		0.0737	0.6876	0.5736	0.5463	0.4227	0.9729	**0.0035**	**0.0339**	0.9207	0.5600
Three previous years			0.7643	0.1636	0.4768	0.4934	0.5836	**0.0022**	0.0780	0.7049	0.7336
Four previous years				0.1690	0.8465	0.3997	0.6104	**0.0034**	0.1151	0.4994	0.9814
Five previous years					0.8741	0.6863	0.5146	**0.0043**	0.0904	0.4163	0.7799
Six previous years						0.6970	0.7537	**0.0054**	0.1133	0.4761	0.6888
Seven previous years							0.7649	**0.0011**	0.1012	0.4182	0.7526
Eight previous years								**0.0007**	0.1666	0.4400	0.6769
Nine previous years									0.1783	0.3020	0.7085
Ten previous years										0.2800	0.5392
Eleven previous years											0.5136

Table 2.1.: p-values sequential testing HBV IR Netherlands from 2001 to 2012.

The European Medicines Agency guideline requires considering data from the three previous years into account. The comparison should be done for each individual blood/plasma collection center such that significant trends can be identified. In addition the EMA request for discussion on the results found. Besides the global trend analysis of the incidence rate we can also check for regional differences between different BCC's. The regional comparison is done by testing the null hypothesis that the numbers of infections in a region are comparable against the alternative that these numbers are significantly different.

For The Netherlands there are four regions, North-West, North-East, South-West and South-East. We define $X = (x_1, x_2, x_3, x_4)$ with x_j the number of infections in region j. We can model the vector X as a multinomial random variable with parameters (n, θ), where n is the total number of

infections and $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$ where θ_j is the probability that an infection comes from region j= 1, 2, 3, 4 with $\sum_{j=1}^{4} \theta_j = 1$.

The number of donors in each region is different and so is the expected number of infections, therefore say k_1, k_2, k_3, k_4 are the number of donors in the region and $K = \sum_{j=1}^{k} k_j$ then we have the proportion of donors that have an infection in a specific region. We can test this with the null hypothesis stating that the infections are distributed evenly in regions against an alternative hypothesis as in (2.8).

$$\mathrm{H}_0 : \theta = \left(\frac{k_1}{K}, \frac{k_2}{K}, \frac{k_3}{K}, \frac{k_4}{K}\right) \text{ versus } \mathrm{H}_a : \theta \neq \left(\frac{k_1}{K}, \frac{k_2}{K}, \frac{k_3}{K}, \frac{k_4}{K}\right) \tag{2.8}$$

For the test we again use the likelihood ratio test statistic and in this regional testing case this is as in (2.9).

$$T = \sum_{j=1}^{4} x_j \log \frac{x_j}{n} - \sum_{j=1}^{4} x_j \log \frac{k_j}{K} \tag{2.9}$$

The results for the testing of regional differences are in Table 2.2 where a zero indicates no infection occurred in a specific year for a particular infectious disease. Therefore if we choose a maximum acceptable p-value of 0.05 we see that for HBV in 2001 there is evidence that there are differences in the incidence rates across regions.

Year	HBV	HIV	HCV
2001	**0.0472**	0.5687	0.7278
2002	0.2336	0.1943	0.2630
2003	0.2278	0.7361	0
2004	0.1875	0.2016	0.5102
2005	0.7299	0.4888	0.2332
2006	0.4710	0.6527	0.8446
2007	1.0000	0.1503	0.7357
2008	1.0000	0.7284	0
2009	0.5111	1.000	0
2010	1.0000	0.4810	0
2011	0.8853	0	0
2012	0.9054	0.8674	0

Table 2.2.: p-values for regional differences in the Netherlands.

The results from Table 2.2 are only from that specific year and its infections, however the sum of infections and donors over a certain period can also be tested with the same hypothesis stating that the infections are distributed evenly in the regions over a period of years. The results by summing over more years for HBV are in Table 2.3. The results for HIV and HCV can be found in Appendix Section A.3.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	**0.0033**	**0.0129**	0.4403	0.5022	0.1808	0.7783	0.6547	0.1236	0.234	0.8731	0.9138
Two previous years		0.1561	0.8558	0.5996	0.4429	0.6728	1.0000	0.3933	0.3889	0.9695	0.9437
Three previous years			0.9743	0.8873	0.7675	0.5350	0.8265	0.5463	0.2465	0.6223	0.9868
Four previous years				0.8778	0.7027	0.8300	0.5670	0.8166	0.3791	0.5042	0.6025
Five previous years					0.6600	0.7425	0.7104	0.8261	0.6813	0.6135	0.5156
Six previous years						0.6859	0.7192	0.7174	0.7175	0.8704	0.5896
Seven previous years							0.6939	0.7134	0.5569	0.8914	0.8080
Eight previous years								0.7825	0.6105	0.7088	0.8827
Nine previous years									0.7028	0.7840	0.7259
Ten previous years										0.8509	0.7309
Eleven previous years											0.8102

Table 2.3.: Regional tests for HBV with data from previous years.

Furthermore the incidence rates of the infectious disease in a region can be tested the same way as in Table 2.1. The test results of the regions give insight in which regions have the same trend as the global incidence rate and which regions do not. For each test we can consider the data of multiple years. That would mean we have a table with test results for each region and for each infection. In Table 2.4 we took into account the data of the past three years as required by the EMA.

	2004	2005	2006	2007	2008	2009	2010	2011	2012
HBV Region 1	0.0600	0.2513	0.7817	0.7550	0.1125	0.9772	0.4195	0.1424	0.9798
HBV Region 2	**0.0079**	0.5865	0.1059	0.6518	0.9981	**0.0084**	0.6319	0.8851	0.4609
HBV Region 3	0.7133	0.3943	0.8993	0.6446	0.5601	0.1174	0.6131	0.5890	0.9666
HBV Region 4	0.9823	0.8885	0.8030	0.9163	0.3025	**0.0132**	0.1779	0.6423	0.9757
HIV Region 1	0.5522	0.6641	0.9820	0.8903	0.3087	0.8120	0.8275	0.4129	0.8321
HIV Region 2	0.5888	0.6026	0.5162	0.5981	0.5160	0.5190	0.5933	0.5891	0
HIV Region 3	0.3095	0.5258	0.1053	0.3110	0.3056	0.8117	0.6019	0.6008	0.5162
HIV Region 4	0.5438	0.2276	0.4172	0.2968	0.4209	0.4245	0.4095	0	0
HCV Region 1	0.5981	0.5158	0.5232	0.4045	0.4153	0.5934	0	0	0
HCV Region 2	0.1507	0.4189	0.8301	0.3077	0.6020	0.5928	0	0	0
HCV Region 3	0.4111	0.4078	0.0936	0.5249	0.4169	0.4206	0.5938	0	0
HCV Region 4	0.1030	0.5926	0.1077	0.3405	0.4136	0.4229	0	0	0

Table 2.4.: p-values sequential test for all regions and all infectious diseases.

Table 2.2 showed that there was no strong evidence that the incidence rates across the regions for HBV in 2009 were different. Table 2.4 however shows that in 2009 in regions 2 and 4 the incidence rate is different from the incidence rate of HBV in previous years with strong evidence as the p-value is smaller than 0.05. Taking into account more historical data we get one more remark of the incidence rate of a disease in a specific region. This in in 2006 for HCV in region 4, the p-values for this region are with 4 years of data 0.0309 and with 5 years of data the p-value is 0.0254. These results are not shown in any table, as this would result in many tables.

A topic that has not been covered yet are the first time donors, the individuals that want to become a blood donor are screened first. If an infection occurs with the first donation, it is recorded and the specific person can not become a donor. The proportion of infected new donors can change over time. For the Netherlands, prevalence data from 1995 onwards now is known from the annual reports from Sanquin. The number of donors however is not entirely well documented, therefore the numbers from 2001 to 2012 are used for the prevalence rates in Figure 2.3. In Figure 2.4 the exact number of identified infections for the first time donor population which will exceed the upper control limit is added and there is a significant increase in the prevalence of HIV infections in 2007 while for the other infections this number of donors is more stable. For the upper bound again the significance of $\alpha = 0.01$ is used.

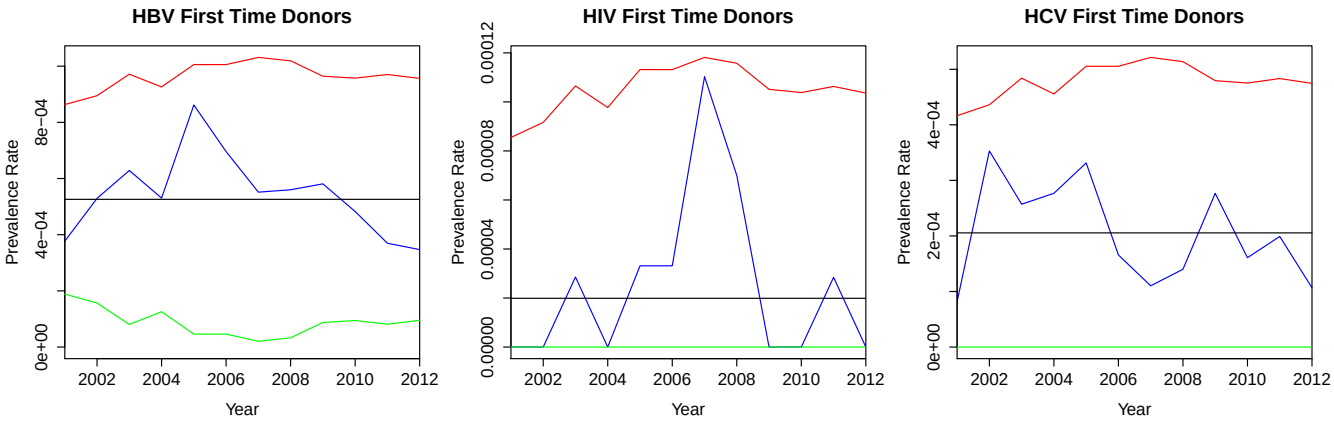

Figure 2.3.: Average rate and bounds for the prevalence of HBV, HIV and HCV.

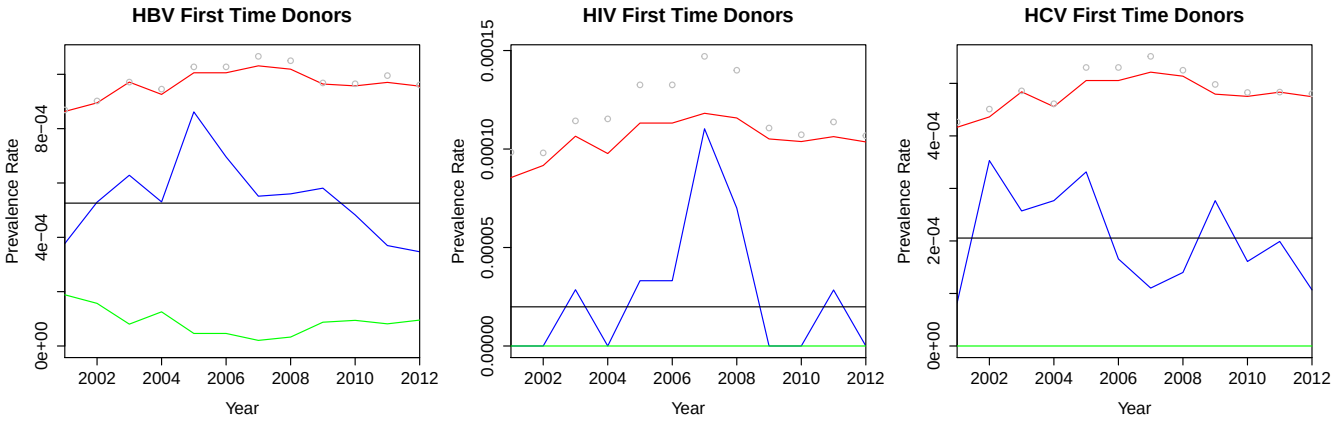

Figure 2.4.: Exceeding number of infections for the prevalence of HBV, HIV and HCV.

2.4. More insights

In this chapter we have seen a basic method to monitor the observed incidence rate of an infectious disease. We have set up a control chart to mark the observations with a upper control limit based on a significance level and with regard to multiple testing. The lower control limit is put down to zero infections each year. The annual data from a country can be monitored that way.

The incidence rate and prevalence rate can be monitored in a chart and a test can be performed to check whether a specific year is not in line with the other years. We also saw a test to specify if the incidence rate in a specific year has differences across regions. For all these tests historical annual data can be included and there is a guideline stating that three years is a good range. However for the first time donor population there are no tests performed on the prevalence rate.

The results of this approach in the previous section should be explained as this might look that there are many fluctuations in the blood donation process. We saw an increase in positive donors with the disease HBV in the year 2009. The nuclear acid test was introduced in November 2008 and used across the Netherlands around January 2009 to test the donation from the donors. This test is able to determine the presence of the disease in the window period of this disease. Therefore the group of donors with this disease would have been found, but by using the new test the detection was sooner. This explains the increase of positive donors with HBV in the donor population in 2009. The nuclear acid tests for HIV and HCV were introduced in respectively mid 1999 and at the end of the year 2000.

To determine the impact of the regions or individual blood collection centers the risk ratio was introduced in Janssen et al. (2009). The risk ratio (RR) is the relative risk increase caused by one blood/plasma collection center and can be derived from the incidence rate of the total population (λ_t) and the incidence rate of the reference population (λ_r). Assume one BCC has a proportion δ of the total population that has an increased incidence rate of exactly $R \cdot \lambda_r$, then the risk ratio is in (2.10).

$$RR = \frac{\lambda_t}{\lambda_r} = \frac{R \cdot \delta \cdot \lambda_r + (1-\delta) \cdot \lambda_r}{\lambda_r} = \frac{\lambda_r \cdot (1 + (R-1) \cdot \delta)}{\lambda_r} = 1 + \delta \cdot (R-1) \tag{2.10}$$

The risk ratio can be useful to further investigate the impact of one center on the global incidence rates. A different ratio that can be calculated is the incidence rate ratio, the ratio between two incidence rates. For example the ratio from the rates from a regional and the global population in a specific year or over more years. Furthermore the ratio can be set to compare the ratio of the rate of one year with the rate of multiple years, therefore if there are infections within a year for a certain region this ratio gives the indication whether the incidence rate of this region is exceeding.
.

Another approach is to determine certain thresholds for each region or for a individual center. Alarm levels can be set on a number of allowed infections. This has as disadvantage that it depends on the size of the centers. It is unlikely to set an alarm at the level of one single positive donor, which can occur by coincidence on any center. In particular when there are zero positive donors over a longer amount of time.

To answer the research questions for this thesis we need improvements to work with the possibility we have many years with zero positive donors. Especially when we look at individual centers or smaller regions when alarm levels can be set to one single positive donor. As the number of positive donors is stabilizing we want to be able to detect small or large changes in blood donation process.

We will see that identifying changes might become more difficult with the sequential character in the current monitoring and testing strategies. The regional tests and annual tests on the incidence rate are set with a particular approach to detect annual or regional differences. The methods described in this chapter are currently in use as these methods represent the guidelines set by the EMA.

The guidelines for the blood donation process has not yet been linked to other methods from the field of statistical process control, in the next chapter we try to establish that link.

3. Statistical process control

In this chapter, literature on statistical process control will explain the use of models for monitoring the process and we present the specific patterns that one may wish to detect while monitoring the process. In Chapter 2 we have seen the current methods to monitor the blood donation process and we noticed that other methods from the field of statistical process control are not explored.

Furthermore, we will present mathematical details of the underlying probability models and mention techniques to test for patterns. These techniques include hypothesis and testing monitoring strategies by using likelihood ratios. There is a group of charts that can help visualizing the processes using specification and control limits. We will also discuss visual tools (the so-called control charts) and performance measures for monitoring strategies.

Note that for the blood donation process the basic level of monitoring is to look at one specific infection at one specific region or center and at only one donor or donation type. Later we briefly indicate how to extend these levels, using methods for spatial statistics and multivariate analysis.

3.1. Monitoring

The field of statistical quality or process control came alive after the book in 1931 by Shewhart, Shewhart (1931). However the standard settings do not suffice in the modern control of the processes, Di Bucchianico and Van den Heuvel (2015). Despite the name statistical process control, the field is not about controlling but it is more about monitoring. Monitoring is checking whether the process is in control, which mathematically can be done by testing hypotheses. Monitoring is often also referred to as surveillance. Monitoring can also be used to detect changes in the disease status within a population as well as movements in different patterns in the process.

There are two types of problems referring to time which can be categorized in Phase I and Phase II problems. Finding unusual patterns in past data is referred to Phase I problems, where it is important to detect whether a statistically out-of-control situation has occurred. The Phase II problems are different from Phase I and found in on-line detection of the out-of-control-situations.

Phase I uses a retrospective view with a data set with past information and Phase II uses an ongoing data stream. Also the goal in Phase I is to estimate the data and find standards, where as for Phase II, the process is ongoing and the data can be analysed and interpreted on-line. Phase II problems relate to determining changes in the process either with or without intervention.

For this monitoring, or also called surveillance, there is an active and passive state, see Frisén (2003, 2009). For active surveillance, an alarm can interrupt the process, where for passive surveillance, actions at an earlier time point do not affect the process, see Frisén and De Maré (1991).

Before we can state specific tests and hypothesis it must be clear what we wish to detect. Using past data to test whether a process is or was statistically in control during the time steps can be done in different ways, see Does and Schriever (1992). The interest can also concern the changepoint from where the process was no longer in control, Hawkins et al. (2003). This changepoint can be

an isolated case, better known as an outlier or it can indicate the start of a trend. Besides the single changepoint, there can also be multiple changepoints. In general problems with changepoint formulations are hard to distinguish whether it is a Phase I with estimated data or Phase II problem with ongoing data.

Besides the framework for our model the process of blood donations needs a specific framework for detecting patterns or specific changes in the monitoring of infectious diseases. The fluctuations within the donor population are generally in-control, which seems valid considering the historical data. However we can use the tests to detect major changes in distributions or increments in the parameter(s).

Interesting fields are the detection of the trend and detecting possible outliers in global or local level. To do this likelihood ratio tests are derived in Janssen et al. (2009). As the EMA has the requirement to do the analysis over a period of 4 years the article implements the likelihood ratio tests on incidence rates EMA (2010). From the point of view of the epidemiologists the interesting part is the (change of) risk within the donor population, where for process minded persons the stability of the process itself is more important. The tests described focus on the incidence rate. Besides changes in the incidence rate it may be that there are changes in the underlying probability distribution which can lead to changes in the risk.

The monitoring strategies should be able to 'start over' and detect changes after a change has occured, e.g. if a new medical test is applied. A new test does not always imply more infections will occur but the system has a certain change. See Table 3.1 for the overview on this section.

Problem Phase	**Time**	**Other**
Phase I	Retrospective	Seen in Chapter 2.
Phase II	On-line	Active and passive state. Active, interruption possible. Passive, no interruption.

Table 3.1.: Monitoring overview

3.2. Models in SPC

We need to extend the current framework as presented in Chapter 2 in order to be able to answer the remaining questions and generate new insights. Therefore we start from scratch and first work out the mathematical details of the approach used in Section 2.1, to make this model more clear. The framework will be extended with another model, commonly used in zero-defects or high yield processes, see Xie et al. (2002). We will show that this new model is more applicable to the blood donation process.

3.2.1. Model 1: incidence counts per time unit

This model considers the data with predetermined, fixed time intervals, e.g. for that year. If the time unit is chosen to be one year then this corresponds to the format countries annual data must

report to the EMA. Mathematically this can be modeled as a rate. Since infections and population sizes differ per time interval, the incidence rate is determined by these infections and population sizes. The rate for each time step i is written as a vector component X_i. Over a period of n time steps the incidence rate vector becomes as in (3.1). We assume that the incidence rates X_i are independent and identically distributed with some distribution function F. The stability of the process is expressed through the common distribution function F.

$$X_1,\ X_2,\ ...,\ X_n \sim F \tag{3.1}$$

Specific for the project regarding the donor population and for this first model we assume that each time step is one year and we assume the incidence rate over this period of n years to be Poisson distributed, see (3.2) and (3.3) for the probability mass function.

$$X_1,\ X_2,\ ...,\ X_n \sim Pois(\lambda) \tag{3.2}$$

$$\mathbb{P}(x;\lambda) = \frac{e^{-\lambda} \cdot \lambda^x}{x!},\ x = 0, 1, 2, ... \tag{3.3}$$

The Poisson distribution has one parameter only, so the mean and the variance are directly related. In fact, they are even equal. It has been observed in practice that count data do not always have this property. For a better fit when the variance is larger than the mean (this is known as overdispersion), we need to use another distribution instead of the Poisson distribution. The negative binomial distribution is widely used for this purpose, see e.g. Ross and Preece (1985). It has a second parameter to adjust for the greater variability in the data set without changing the mean.

3.2.2. Model 2: number of donations between infections

The advantage of the first model is to get a good overview per time unit. However the model has disadvantages if counts are few or when the time unit is chosen small. Detecting trends and changes in specific processes with this model is quite slow. Therefore another model is introduced. The second model is not based on counts like the first model, but on the number of donations between (multiple) infections.

Assume these numbers are independent and identically distributed with some distribution function F. Define T_i to be the number of donations for each step i. When the incidence rate λ for a donor population of a infectious disease is constant there is a constant probability p that a single donation is tested positive for a infectious disease.

For example, an exponential distribution can be used to estimate the number of donations between infections, see (3.4). The exponential distribution is a continuous probability distribution with the memoryless property. The discrete counterpart of this probability distribution function is the geometric distribution, then the number of donations until a infection has a geometric distribution where the parameter p gives the probability that an infections occurs, see (3.5). The geometric

distribution also has the memoryless property. The memoryless property can either be an advantage or disadvantage since it makes it easy to work with but may not be realistic in practical situations.

$$T_1,\ T_2,\ ...,\ T_n \sim Exp(\lambda) \tag{3.4}$$

$$T_1,\ T_2,\ ...,\ T_n \sim Geo(p) \tag{3.5}$$

The advantages of this model over the first model is the quicker detection of trends and changes in high yield processes, see Xie et al. (2002). See Table 3.2 for the overview on this section. As already mentioned in Section 3.2.1, the negative binomial distribution has advantages for modelling the process, as seen with overdispersion the Poisson distribution. We now see another not related use of this model. The count until r infections in a sequence of independent Bernoulli trials is related to this model.

Therefore let X be the cumulative count of donations inspected until the observation of r infections is found. Then X follows a negative binomial distribution with parameters p and r, see (3.6).

$$X \sim NB(r, p) \tag{3.6}$$

Note that when $r = 1$, the negative binomial distribution is a geometric distribution, see also (3.7) and (3.8).

$$\mathbb{P}[X = i] \ = \ \binom{i-1}{r-1} \cdot p \cdot (1-p)^{i-r},\ i = r,\ r+1,\ ... \tag{3.7}$$

$$G(x; p) \ = \ p \cdot (1-p)^{x-1},\ x = 1,\ 2,\ ...,\ n,\ ,\ ... \tag{3.8}$$

Model 1	Counting infections per time unit.
Distribution	Poisson.
Advantage	Get a good overview over a chosen time step.
Disadvantages	Slow detection of changes in the process.
	Nothing to 'see' with zero infections.
Model 2	Count of conforming donations.
Distribution	Geometric and negative binomial.
Advantages	Quick detection of changes for zero defect processes.
	Counting donations inbetween $r > 1$ infections.
	Less expected false alarms.
Disadvantage	Working with new 'timescale'.

Table 3.2.: Overview models

3.3. Patterns

For the monitoring framework we need to be more specific about the term 'change' and look over certain patterns. In the epidemiology there is a special interest for the change as in the outbreak of a disease. The focus however will not be on that change, since we assume the outbreak will not be seen in the blood donation process. By setting alarm levels we can detect patterns and we might determine the point where the change occured. Detecting changes and estimating when a change occurred are discussed in various papers, e.g. Frisén and De Maré (1991); Lai (1995); Frisén (2003, 2009).

To detect patterns we look at the basic level of the blood donation process, that is one infection, one center, one donation type and we do not specify a donor type. The specific non-random patterns we want to be able to detect are shifts that are temporary or persistent, trends, a repeated movement in the observations or a lcak of movement in the observations. Additional, mixtures of patterns may take place, which is hereby briefly mentioned. In Table 3.3 the characteristics of the different non-random patterns is listed.

Pattern	Characteristic
Cyclic	Continuous repeated movement.
Shift	A (sudden) huge shift.
Trend	A continuous small drift.
Epidemic	A temporary huge shift.
Stratification	Almost constant values.

Table 3.3.: Patterns in blood donation process

Some numerical examples of the patterns based on a two year period with a stable donor population, with 100000 persons, say where (made-up) infections occur are shown in Table 3.4. In this example for all changes on an annual report, the incidence rates of the donor population in both years will be the same.

In the example we see that a shift occurs where an infection is found in 1 of every 100000 persons in the first periods of the year but in the last periods the average is increased to 2 of every 100000 persons. The trend in the example is given by an increase of the infections in these two years. The epidemic pattern shows a temporary time of 4 periods where no infections occur.

Period	1-1	1-2	1-3	1-4		Year 1		2-1	2-2	2-3	2-4		Year 2
Shift	1	1	2	5		9		3	2	2	2		9
Trend	1	0	1	0		2		1	0	1	1		3
Epidemic	1	2	0	0		3		0	0	1	2		3

Table 3.4.: Numerical example of patterns.

More mathematically we define the states of the process as:

- State 0: the system is in-control.
- State 1: the system has changed.

We specify τ as the (unique) time step at which the system changed or a pattern started and consider the observed mean of the system by $\mu(t)$ for each time step $t = 1, 2, ...$ We can then

mathematically formulate a persistent change, based on unacceptable values as in (3.9).

$$\begin{aligned} \mu(t) &= \mu^0 \quad (\text{for } t = 1, ..., \tau\text{-}1) \\ \mu(t) &= \mu^1 \quad (\text{for } t = \tau, \tau{+}1, ...) \end{aligned} \tag{3.9}$$

In (3.9) we have the acceptable value of the mean μ^0 and the unacceptable value of the mean μ^1, which will be known values. Testing for patterns in the blood donation process can be done by setting hypothesis that can specify what is a natural pattern against an unnatural or unwanted situation. Control charts can help visualizing the model and the characteristics. There are some useful control charts for detecting patterns, we will explain the control charts and their use in the next section, e.g. see Montgomery (2005).

3.4. Control charts

In statistical process control, statistical methods are applied to monitor the process. SPC can be applied to monitor the number or frequency of conforming and non-conforming products. For the blood donation process this can be seen as the donation without or with an infection. Tools for the SPC are control charts to detect patterns in either the proportion of the mean or the variation of the process. The following control charts will be explained, Shewhart, CUSUM, EMWA and CCC-r. Setting up a specific control chart where the mean and standard deviation are used can be generally scheduled as follows: (see Gitlow et al. (1989))

- Obtain the characteristics of the process by observation.
- Calculate the process mean or stable situation, this is the center line (CL).
- Calculate the standard deviation of the process.
- Calculate an upper and lower control limit based on the mean and standard deviation.
- Plot the process characteristics on the chart.
- If points fall outside the limits, reason and decide on the points and if applicable modify the control limits and center line.
- Continue to add the new measurements in the control chart.

For other charts a similar approach holds where other calculations or parameters are used.

3.4.1. Shewhart

The Shewhart control chart has already been described in Section 2.1. This chart provides us with a good overview of incidence rates of infectious diseases over time, hereby limits can signal changes in the process. The upper and lower control limits, as described in (2.2), can be set at 3 standard deviations of the (observed) mean respectively up and down. In the Shewhart chart the stability of the process can be visualized by making a Shewhart chart for the mean and for the variance. Both models, see for model 1 in Section 3.2.1 and for model 2 in Section 3.2.2, can be monitored by the Shewhart chart. Therefore there are many options available regarding the blood donation process. Specific settings and details for this process will be discussed later on.

Detecting changes is done in a statistically surround way by using hypothess and statistics. We can use the Neyman-Pearson lemma, which states that for a simple test the likelihood ratio test is the most powerful test of size α. Recall the likelihood-ratio and log-likelihood, see (3.10) and (3.11) for Θ_0 and Θ_a with $\theta \in \Theta$, the partition of the parameter setΘ into two disjoint sets Θ_0 and Θ_a.

$$S = \frac{\sup_{\theta \in \Theta_a} L(\theta)}{\sup_{\theta \in \Theta_0} L(\theta)} \tag{3.10}$$

$$T = \log\left(\frac{\sup_{\theta \in \Theta_a} L(\theta)}{\sup_{\theta \in \Theta_0} L(\theta)}\right) = \ell\left(\hat{\theta}_a\right) - \ell(\hat{\theta}_0) \tag{3.11}$$

Based on the likelihood-ratio the UCL bound for the Shewhart control chart is as seen in Section 2.2. If the change of the observations (also referred to as the stopping time) is known in the Shewhart procedure it has the form in (3.12) where we set the critical limit h, see e.g. Antoch and Jarušková (2002).

$$\tau = \inf\left\{ n \mid \log \frac{f_a(X_n)}{f_0(X_n)} \geq h \right\} \tag{3.12}$$

3.4.2. Generalized likelihood ratio

Besides the Shewhart procedure we have the cumulative sum (CUSUM) procedure introduced in Page (1954) and see Hawkins and Olwell (1998) for an comprehensive overview. The CUSUM procedure is a special case for a specific alternative hypothesis from the generalized likelihood ratio (GLR).

Consider the sum S_n for $n \geq 2$ as defined by the resursion in (3.13), with $S_1 = 0$.

$$S_n = \max(0,\ S_{n-1} + X_n) \tag{3.13}$$

The test statistic based on the sum is for n time steps, given by $T_n = \sum_{i=1}^{n} t_i$. For each time step i we have the log-likelihood ratio $t_i = \ln \frac{f_a(X_i)}{f_0(X_i)}$ for the observations X_i. The decision function g_n is the difference between the value of the log-likelihood ratio at time step n and the current minimal value of the statistic, see (3.14). The decision is to compare it with the threshold h.

$$\begin{aligned} g_n &= T_n - m_n \geq h \\ m_n &= \min_{1 \leq j < n} T_j \end{aligned} \tag{3.14}$$

This can be set up as a stopping time decision, see (3.15). In the CUSUM procedure the past of the process is taken into account.

$$\begin{aligned} \tau &= \min\{\, n \mid T_n - \min_{1 \leq j \leq n}\ T_j \geq h\} \\ \text{with } T_n &= \sum_{i=1}^{n} \log \frac{f_a(X_n)}{f_0(X_n)} \ \textit{and}\ S_1 = 0 \end{aligned} \tag{3.15}$$

3.4.3. EMWA

Besides the Shewhart and CUSUM control charts there is another chart we need to explain, namely the exponentially weighted moving average (EWMA) chart, see in Shiryaev (2010), which is defined by a recursion, see (3.16).

$$V_i = \lambda \cdot X_i + (1-\lambda) \cdot V_{i-1},\ V_0 = 0 \text{ and } 0 < \lambda < 1 \tag{3.16}$$

For $\lambda = 1$ we get the Shewhart chart, however when $\lambda \to 0$ we obtain a CUSUM procedure. The CUSUM procedure is better in detecting small changes than the Shewhart chart. Therefore the EMWA chart has the advantage of the performance of detecting small changes, which is nearly as good as the CUSUM, and the robustness against deviations from normality, see e.g. Montgomery (2005).

3.4.4. CCC-r

A different approach was first developed by Calvin (1983) and given the name by Goh (1987). The cumulative counts of conforming chart (CCC), see Xie and Goh (1992); Xie et al. (1998, 2002); Chan et al. (2003), is used to monitor high yield processes. The procedure makes use of the large number of conforming items and counts the consecutive numbers of conforming items between nonconforming ones. In this thesis that will consider the number of donations inbetween a donation where a infection has been detected. The parameter r gives the number of nonconforming items (here infected donations) to count before counting the conforming items, which may be chosen larger than one for different situations.

The procedure of the standard CCC chart is similar to the procedure of the Shewhart control chart, however the control limits are determined in a different way. The number of conforming items follows a geometric distribution, see (3.2). Therefore if we let n be the number of items to be observed before a nonconforming one is found, then we have $n-1$ conforming donations and the n'th donation is tested positive for an infection. The probability of this is as in (3.17) and the mean of the number of conforming donations, used as the center line is $CL = \frac{1}{p}$.

$$G(k,p) \ = \ p \cdot (1-p)^{k-1}\ ,\ k = 1, 2, ..., n \tag{3.17}$$

An upper and lower bound can be constructed such that the false alarm probability α for a single decision is acceptable, see (3.18).

$$\alpha \ = \ \mathbb{P}[\text{False Alarm}] = 1 - \mathbb{P}[LCL \leq X \leq UCL] \tag{3.18}$$

The control limits for a geometric distribution can be set up with parameters α and p, see (3.19) and (3.20).

$$\text{UCL}=\frac{\ln(\frac{\alpha}{2})}{\ln(1-p)} \tag{3.19}$$

$$\text{LCL}=\frac{\ln(1-\frac{\alpha}{2})}{\ln(1-p)} \tag{3.20}$$

We see that these control limits are highly asymmetric. If the parameter r, the number of non-conforming items, is larger than 1 we have a negative binomial distribution and we have different control limits. Let X be the cumulative count of conforming items until we have observed r non-conforming items; the probability distribution is in (3.7). The cumulative distribution function of X can be written as in (3.21).

$$\text{F}(n,r,p)=\mathbb{P}[X\leq n]=\sum_{i=r}^{n}\binom{i-1}{r-1}\cdot p^r\cdot(1-p)^{i-r} \tag{3.21}$$

It is possible to calculate an explicit form for $\text{F}(n,r,p)$ for small values of the parameter r. For $r=2$ we have (3.22).

$$\text{F}(n,2,p)=p^2\cdot[\frac{1-(n-1)\cdot(1-p)^n-n\cdot(1-p)^{n-1}}{p^2}]=1+(n-1)\cdot(1-p)^n-n\cdot(1-p)^{n-1} \tag{3.22}$$

For other values of r we are also able to calculate the complicated form's with a computer program. With the cumulative distribution we obtain the control limits for the $CCC-r$ charts. The formulas for the upper and lower control limit are in (3.23) and (3.24) and can be calculated for an acceptable risk of the false alarm probability α for a single decision.

$$\text{F}(UCL,r,p)=\sum_{i=r}^{UCL}\binom{i-1}{r-1}\cdot p^r\cdot(1-p)^{i-r}=1-\frac{\alpha}{2} \tag{3.23}$$

$$\text{F}(LCL,r,p)=\sum_{i=r}^{LCL}\binom{i-1}{r-1}\cdot p^r\cdot(1-p)^{i-r}=\frac{\alpha}{2} \tag{3.24}$$

For small values of p we get large values for the center line, where the cumulative distribution has the value of $\frac{1}{2}$, which might make it not appropiate to use the $CCC-r$ values with a large r value.

3.5. Performance

We have seen several models, the patterns and some important control charts. We define the performance measures for the control charts to get more knowledge about their performance so that we can see the differences between the models. The control charts have to be able to determine the patterns and the moment the process is in-control or due to a change it might go out-of-control.

One measure that is being used to quantify the performance is the Average Run Length (ARL). We distinguish the in-control ARL (ARL_{in}) and the out-of-control ARL (ARL_{out}). The ARL is

most frequently used for the control charts. For example we can determine the ARL for a $CCC-1$ or Shewhart $\overline{X}$ control chart, see (3.25), where X has a geometric distribution with probability p.

$$\text{ARL} = \sum_{n=0}^{\infty} P[X > n] = \sum_{n=0}^{\infty} (1-p)^n = \frac{1}{p} \tag{3.25}$$

The expected ARL can also be calculated for the $CCC-r$ control charts. We will go into more detail for the ARL of the first model and the ARL for the second model later in this thesis. More on the ARL and a discussion of some shortcomings can be found in Kenett and Pollak (2012); Margavio et al. (1995); Frisén (2003); Frisén (2011).

Run lengths are skewed distributions, the run lengths are often approximated by a geometric distribution. The standard deviation of the run lengths (SRL) is another measure for the run length. The SRL can give, in collaboration with the ARL, an indication of how the run lengths behave.

Calculations of characteristics of run lengths becomes complicated when run rules are added to a control chart, see for example in Montgomery (2005). The run rules play a role in control charts and are able to give warnings if points have certain behavior. See for example in Brook and Evans (1972) where the method was first presented in the context of run lengths for CUSUM charts. The method and calculations can be applied on the run lengths of other control charts as well. By adding run rules, the ARL can change.

4. Design of the simulations

A simulation program was constructed in order to obtain an overview of the blood donation process and to be able to make changes in the process. As one of the research questions is what the differences are in the blood/plasma collection centers or in the donation and donor types, these aspects should be part of the simulation. Besides the different inputs the simulation should also be able to handle the different models and monitoring strategies. With the completion of the simulation program certain patterns can be inserted, therefore we will be able to determine differences in the monitoring strategies. The framework of the simulation program can furthermore be the base for or help with further research.

4.1. Description simulation

The simulation model will realistically mimic the process of blood donations and the occurrence of infections. In this process there are different blood/plasma collection centers involved where different types of donations take place. Furthermore for these different donation types different types of donors are involved. The simulation model is constructed in *R*, therefore we work with the so-called data frames.

Centers database, creates a data frame with for each center an average number per time step of donation types for each type of donation and the size of the donor pool for the specific type. These data can either be generated or determined in advance.

Input:	Number of donation types, number of centers.
Output:	List with estimated sizes for donation types and donor population.
Functions:	Generate database, generatedonationtype, generatedonorpool.

Table 4.1.: Constructing Centers database

The donation types can be generated with different approaches. For the purpose of this thesis the number of donations for a certain donation type per time step are simulated with a Poisson distribution with a exponential scale for the mean. Hence these average time step numbers are for the first type for example $Poisson(10)$, for the second type $Poisson(100)$, etc. These numbers are enlarged with a random number between 1 and 5 to add extra variability in the size of the centers. Besides these numbers there is a probability of 0.25 that a center does not have the specific donation type. For each donation type the size of a donor pool is created with a similar idea as for the donation type. The size for the donor pool is set, which is able to do the desired number of the donations for each type. See Table 4.2 for a typical setup for the centers database.

Center	DonationsType1	DonationsType2	DonorsType1	DonorsType2
1	250	1000	250	250
2	0	5000	0	1250
3	100	0	100	0
4	50	2000	50	500

Table 4.2.: Example simulated numbers for the Centers.

Donors database, creates a data frame for two type of donors, namely the repeat donors and the first time donors. For each donation type there is a certain group of donors. Here specifications can be made to have first time donors only give a certain donation type and similarly for the repeat donors. This is given by probabilities, i.e. the probability that an donation with a specific type is a repeat donor or a first time donor.

Infection rates can be set with a probability distribution for all centers and donor or donation types. The parameters can be set in a appropriate manner to create different infections rates for each type of donor and type of donation. Here the frequency of the donation type can be involved such that instead of using the donor pool the donor years can be used. See Table 4.4 for a typical setup for the donors database. More about the use of the donor years is in Section 4.3.

Input:	Centers database and the number of infections.
Output:	Database with the probabilities for the type of donor for each donation type and probabilities for an infection for each type of donor.
Functions:	Generate database, generateinfectionrates.

Table 4.3.: Constructing Donors database.

Center	RDType1	RDType2	FTDType1	FTDType2	RDInf1	RDInf2	FTDInf1	FTDInf2
1	0.8	1	0.2	0	0.0002	0.0001	0.0010	0
2	0.8	1	0.2	0	0.0001	0.0001	0.0005	0
3	0.8	1	0.2	0	0.0003	0.0002	0.0002	0
4	0.8	1	0.2	0	0.0000	0.0001	0.0001	0

Table 4.4.: Example simulated numbers for the Donors.

Donations database, creates a data frame for a given number of time steps. These time steps can be chosen as e.g. weeks, months or years. For each donation characteristics are stored, these are the time step of the donation, the type of donation, the center where the donation took place, the type of donor that did the donation and the check for the different infections.

Input:	Centers and donors database and total number of time steps.
Output:	Database with the donations and characteristics time step, donation type, center, donor type and possible infection(s).
Functions:	Generate database.

Table 4.5.: Constructing Donations database.

The database is constructed by first creating the groups of donations, per center and per donation type, out of the Centers database. When the donations for all these groups are done, the donations for the specific time step are completed. For each group of donations the Donors database is used to determine which type of donor did the donation and whether the test of the donation was positive for an infection or not. As an example, see Table 4.6, for a typical (part of the) setup for the Donations database.

Time step	DonationType	Center	DonorType	Inf1	Inf2	Inf3
1	Type1	1	RD	0	0	0
1	Type2	1	RD	0	1	0
1	Type2	2	RD	0	0	0
1	Type2	2	FTD	0	0	0
2	Type1	1	FTD	1	0	0
2	Type1	1	RD	0	0	0
2	Type2	1	RD	0	0	0
2	Type2	2	RD	0	0	1

Table 4.6.: Example simulated numbers for the Donations.

All this information leads to the following overview in Figure 4.1 for the Centers, Donors and Donations databases. The overlying connection between the Centers, Donors and Donations is the time step. For each time step there is for each center a number of donations per donation type and a specific donor population and for this donor type there is at that time step a possible occurence of an infection.

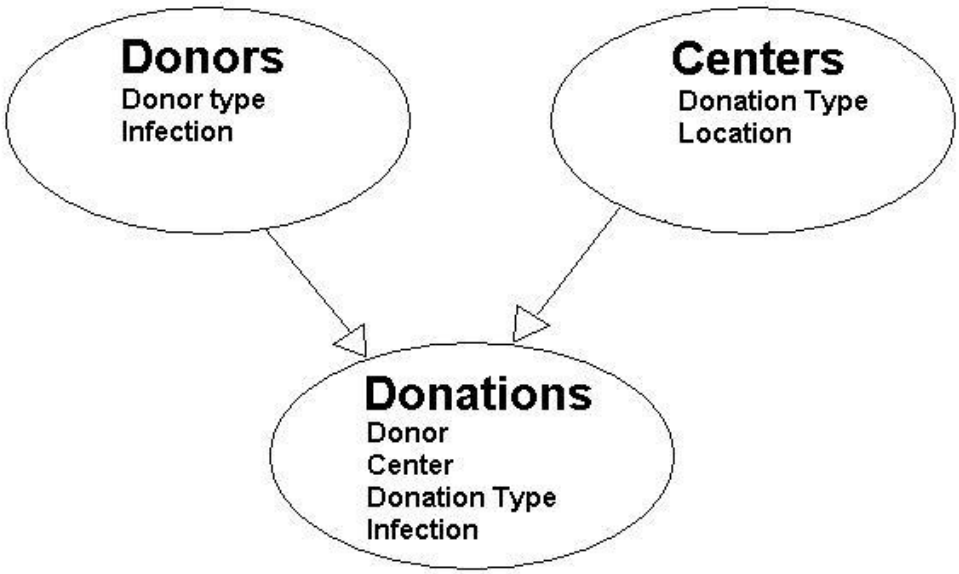

Figure 4.1.: Overview structure Centers, Donors and Donations.

4.2. Totals and structure

Out of the large number of donations the total numbers will play a role. To get all the desired information all the entries of our Donations database must be aggregated. The Donations database has per donation all characteristics stored, however we need to get the specific numbers on different cases.

For each infection the number of infections and the number of donations with one or more infection should be known for each time step, for each center and for each donor/donation type individually. In order to determine the proportion of an infection the numbers of donations in total for each time step, for each center and for each donor type and donation type should be drawn from the total list of donations. All of the specific selections can be recalled by aggregating the specific characteristics in the Donations database.

The simulation is programmed in R (Version 3.1.0), the desired manipulation are performed with the help of the *plyr* package by Hadley Wickham.

For both models the aggregated data are determined. Since the model makes use of data for each year the donations need to be aggregated towards each year. For each donor type, donation type and center the donor population (donor years) should be aggregated with the number of infections. Therefore we have to keep track of the donor years for each center, donor type and donation type. In Table 4.7 we have an example for annual data for a specific center, donor and donation type with 3 infections.

Year	Donor years	Inf1	Inf2	Inf3
1	16163	0	0	0
2	16827	0	1	0
3	16568	0	0	0
4	16859	0	0	1
5	16437	1	0	0

Table 4.7.: Example annual data.

For the second model we need to aggregate the Donations in a different way to extract the numbers between infections. In general we keep the time steps and the columns for the center and the type. Both the number of donations and the number of infections for each step are aggregated. In Table 4.8 we show an example of how the data may look like.

Furthermore there is a method to get the specific number of donations in between multiple infections for each donor/donation type and for each center. Hence the framework for the second model that counts donations inbetween 2 or more infections. For this thesis the simulation model counts the donations between one to five infections for the whole timespan for each center and the specific donor and donation type. These numbers are determined on the aggregated donations. Hence on the time step of a week, which means that if one infection is found in that time step, the number of

Time step	Center	Variable	Donations	Inf1	Inf2	Inf3
1	1	FTDType1	250	1	0	0
1	1	RDType2	3000	0	2	0
1	2	RDType1	1000	1	0	0
1	2	RDType2	1000	0	0	1
2	1	RDType1	500	0	0	0

Table 4.8.: Example Aggregated Data.

donations in that week is evenly divided to the count for and after the infection. If more than one infection occured within the same time step, the number of donations in that time step is again evenly divided, depending on how many infections, and added to the counts of donations for the second model.

The models in combination with the aggregated and annual data from the generated Donations database and with the number of donations between infections gives the entire framework for the analysis.

4.3. Data input

In order to use the simulation in the most realistic scenarios the data input is determined by historical data from the Netherlands provided by Sanquin. We start with looking at the donor population and the donation types.

The probability that a donation has an infection is determined by the donor only. A donation has an infection when the donor is tested positive for an infectious disease. Each infectious disease has an incidence rate for the donor population. The most common donations are the whole blood donation and the blood plasma donation. These types both have their restrictions on the donation frequency and the number of donations each year for every donor. This is a factor that plays a role in the measurement for the incidence rate in the guidelines EMA (2010). Instead of determining each interval between donations for each donor we estimate this by taken into account the frequency of the donations.

	Average frequency	Maximal times allowed	Minimal interval
Blood plasma	5.8	23 times a year	14 days
Whole blood	1.6	5 (men), 3 (women) per year	on call

Table 4.9.: Donation Types

In Table 4.9 we see the main numerical differences between these donation types and as there is a considerable difference in their average frequency we need to take that into account. We use the donation frequency to determine the probability for each donation a donor does, see (4.1).

$$p_{\text{donation type}} = \frac{\text{Incidence rate infectious disease}}{\text{Average frequency donation type}} \tag{4.1}$$

The donor years, as used in Table 4.7 can then be determined, see (4.2).

$$\text{Donor years}_{\text{donation type}} = \frac{\text{Number of donations in time period}}{\text{Average frequency donation type}} \tag{4.2}$$

The measurement for the incidence rate for a infectious disease in the annual reports to the EMA, then becomes as in (4.3). The different donation types can be combined by a linear combination.

$$\text{Estimated incidence} = \frac{\text{Number of positive repeat tested donors in time period}}{\text{Donoryears in time period}} \tag{4.3}$$

For the prevalence rate this does not apply, since first time donors are first screened and can only do a whole blood donation. Although the prevalence rate is quite some factors different then the incidence rate and there is no direct link between these rates we assume that we are in a stable situation for both donor groups. Furthermore specified in assuming a stable situation are the number of donations on a weekly or annual basis, the number of centers and the sizes of the centers.

The number of donations in The Netherlands has been quite stable and over 800.000 donations each year of which the whole blood donations are still most common with approximatly 500.000 donations each year. As there are around 330 centers to donate throughout the Netherlands the size of all centers differ a lot, there are also centers where not every donationtype is donated. After estimating the number of donations at the centers in the Netherlands we see that these number of donations are exponentially distributed over the centers. The total number of donations at the centers differs from a few hundreds up to around 40000 donations in a year in a center.

The incidence rates from HBV, HIV and HCV that are used in the simulation for the repeat donor population are shown in Table 4.10.

Infectious disease	Incidence rate
HBV	1.5
HIV	0.5
HCV	0.05

Table 4.10.: Incidence rates per 100.000 repeat donors

We want to see how the blood donation process behaves in different scenario's, therefore we set up some realistic patterns. We focus on an increase in the incidence rate of a infectious disease by a trend and a shift.

4.4. Methods and charts

We work with a stable situation and we pick one center, one infectious disease, one type of donor and one type of donation to determine further details. The simulation is able to start a blood donation process for a given parameter where the number of time steps is needed. We want to implement the charts and to be able to determine limits and to signal for an alarm.

We will work with the aggregated information from each time step and the annual numbers from the simulated donations. The simulation is able to create new donations for each time step and for as many time steps as preferred. New donations can then be made with changed parameters. For example the incidence rate (or the probability that an infection occurs) can be changed, the number of donations can be changed, the frequency of the donors can be changed as also the donor population can be in- or decreased. After the blood donation simulation has created new donations, the aggregation can be done again.

From Section 4.2 we have the ability to calculate each number of donations between infection(s). These numbers are the input for the $CCC - r$ charts for our second model. With the Quality Control Chart (qcc) package from Luca Scrucca, the control charts we want to use are turned into objects we can use. The function from the qcc package enables us to set up control limits and determine warnings or alarms. The plot-function allows us to diplay the control charts and monitor the behaviour of our data.

For the first model, Section 3.2.1, we wrote a function of our own to monitor the annual information from the blood donation simulation. This function determines the control limits, is able to make a plot and can determine an alarm, when the annual data is exceeding one of the limits for the first time.

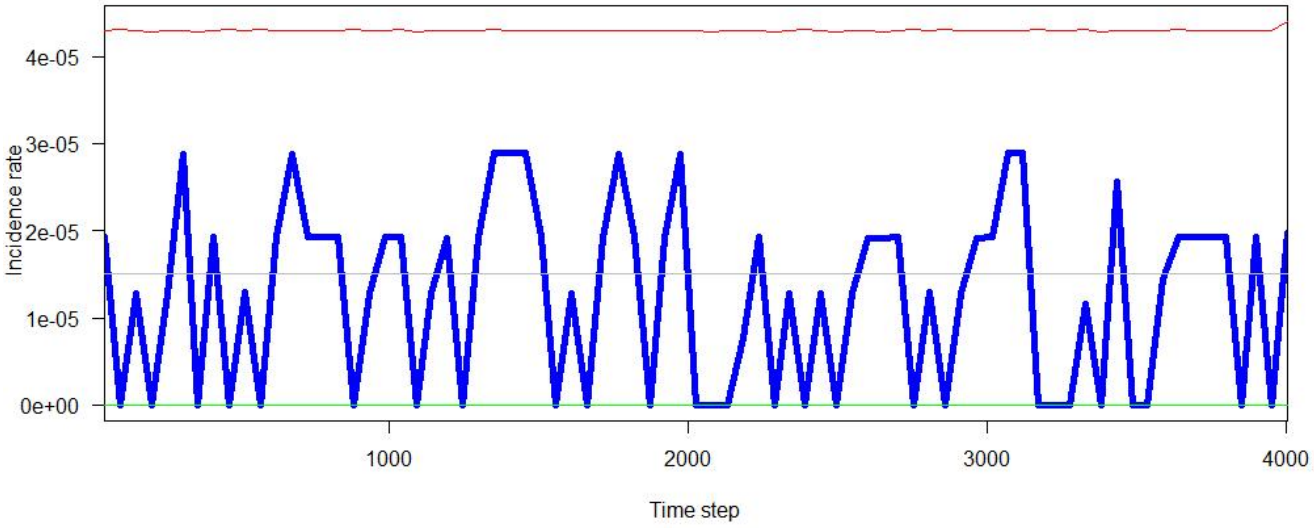

Figure 4.2.: Example of the control chart of the first model.

A technical note to mention is that for this first model is case of year(s) where no infection has occured, when we do find a positive donor the observation becomes the infection divided by the sum of the donor years over the years where no positive donor was, see Figure 4.2 for an example of the control chart.

The objects from the $CCC - r$ charts store the data (numbers of donations), the time steps, the limits, a name given (to identify center, the donor and donation type and infectious disease), the control limits and the violations or points beyond control limits. The object also calculates the mean and the deviation of the data. In Figure 4.3 we have an realistic example of the $CCC - 3$ chart where we set a very high UCL and where there are no runs exceeding one of the limits.

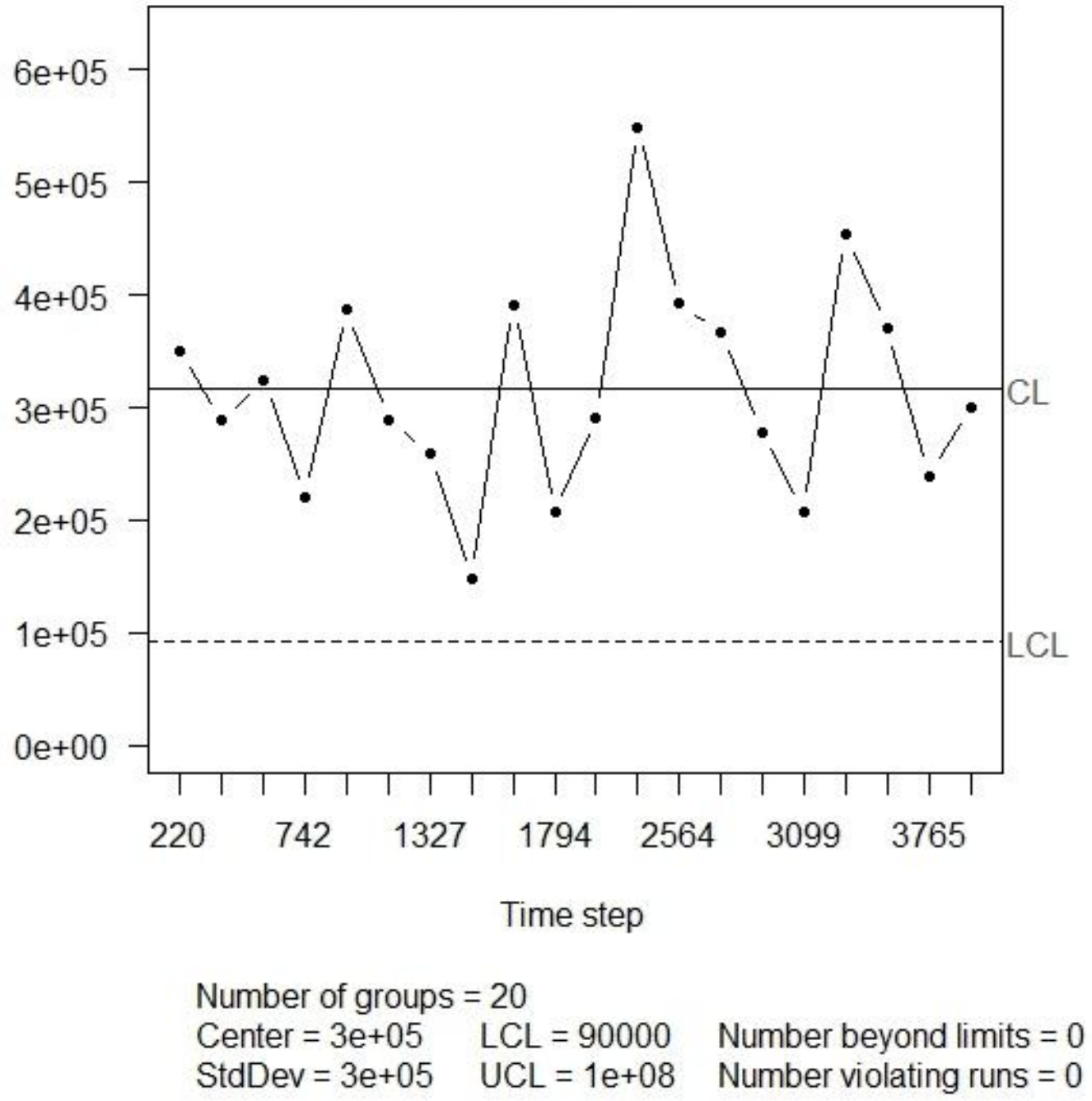

Figure 4.3.: Example of a control chart ($CCC - 3$) for the second model.

Last but not least, after performing a desired number of simulations there is a function that is able to determine the run length of each model. From the previous methods we can get the time steps at which the blood donation simulation process has an alarm for the different models. For all simulations this last function will return the ARL and SRL for each model.

5. Framework for comparing monitoring procedures

In order to determine the ability of both models to detect patterns and to be able to compare them to one another we need to establish a comparison framework. We want to simulate the blood donation process long enough in time steps and simulate many times to know the process can be stable without any false alarms. As we need to work with realistic scenarios we need to get those scenarios by making certain assumptions. To compare the models we need them to behave the same in a stable situation which means adapting the limits of the corresponding control charts.

5.1. Assumptions

First of all, when we assume an incidence rate for the repeat donors either infectious disease we see that the lower control limit for the first model is set to zero, it is actually negative. This will refer to the second model of an upper control limit of infinity. The lower control limit for the first model is determined by the average rate, the annual aggregated donations and α, the for this purposes desired false alarm probability. For our realistic incidence rates, see Section 4.3, the corresponding lower control limit is zero in the first model. That implies we need to set the upper control limit in our second to infinity. As a matter of fact it is more realistic to use no lower limit on the occurences of infectious diseases when the incidence rates are that low. The highest incidence rate of 1.5 in 100000 in our scenario corresponds to such low probabilities that an infection occurs that one positive donor should not give an alarm.

As seen in Section 4.3 we established the frequencies of donation types which we use to determine the probabilities of finding a positive donor at their donation. In Table 5.1 we see these probabilities for the three infectious diseases.

Infectious disease	Incidence rate	p whole blood donor	p blood plasma donor
Hepatitis-B	$1.5 \cdot 10^{-5}$	$9.375 \cdot 10^{-6}$	$2.586 \cdot 10^{-6}$
HIV	$0.5 \cdot 10^{-5}$	$3.125 \cdot 10^{-6}$	$8.621 \cdot 10^{-7}$
Hepatitis-C	$0.5 \cdot 10^{-6}$	$3.125 \cdot 10^{-7}$	$8.621 \cdot 10^{-8}$

Table 5.1.: Probabilities of finding a positive donor per donation.

From these small probabilities we can use the literature from Section 3.4.4 to determine how many donations we need to test before we find an positive donor. We set up a minimal number of time steps, which is three years with respect to the guidelines of the EMA. We compare the fourth year with the first three years. We need a maximal number of time steps which is sufficient for our simulation runs, this is set to 252 years.

We know what typical sizes of blood collection centers are in terms of the number of donations. In order to have realistic scenarios for the number of donations and the type of donation we choose

1600 and 4000 donations each week. That corresponds to 83200 and 208000 donations which can be seen as a relative large blood collection center and a region with a high number of centers. As we have seen the number of times each year the donor comes to the center determines the donor population. In Table 5.2 the corresponding donor population for these number of donations is are listed.

Annual donations whole blood	Number of donors
83200	52000
208000	130000

Annual donations blood plasma	Number of donors
83200	14352
208000	35880

Table 5.2.: Chosen donor populations.

The last assumption we make is to work with the repeat donor population only and ignore the first time donor population. The group of first time donors has typical higher incidences, however we want to concentrate on the more difficult situation with a low incidence rate.

Summary on assumptions:

- We assume a one-sided control limit, hence the lower control limit is set to zero in the first model and this corresponds to setting the upper control limit for the second model to infinity.
- The simulation runs start with 3 year and adds the aggregated annual data to determine the average rate and upper control limit.
- The maximal number of years for the annual data is set to 252 years.
- Annual number of donations are chosen at 83200 and 208000 for both the whole blood and blood plasma donors, respectively.
- We simulate the group of repeat donors only.
- We set the false alarm probability α to 0.05, see (3.18).
- We simulate the blood donation process 1000 times.

5.2. Stable situations

The stable situation we have set up is for a typical large blood collection center with 83200 annual donations. The corresponding donor population we select is 52000 whole blood donors. We let the incidence rate be $1.5 \cdot 10^{-5}$. In this scenario we have a probability of $9.375 \cdot 10^{-6}$ each donation that an infection occurs.

We can determine a numerous of details before running the simulation as we know from Section 4.1 that the number of donations each time step is determined by a Poisson distribution. The expected number of positive donors found each year is $83200 \cdot 9.375 \cdot 10^{-6} = 0.78$ and we know that the expected number of donor years is the number of expected donors. We can then calculate the upper control limit based on the desired false alarm probability α. The upper control limit can then give an indication of how many positive donors within a year should be found to give an

alarm. If we make the false alarm probability smaller we might need one more positive donor on the annual donor population to get that alarm. This setup needs to be simulated for these reasons.

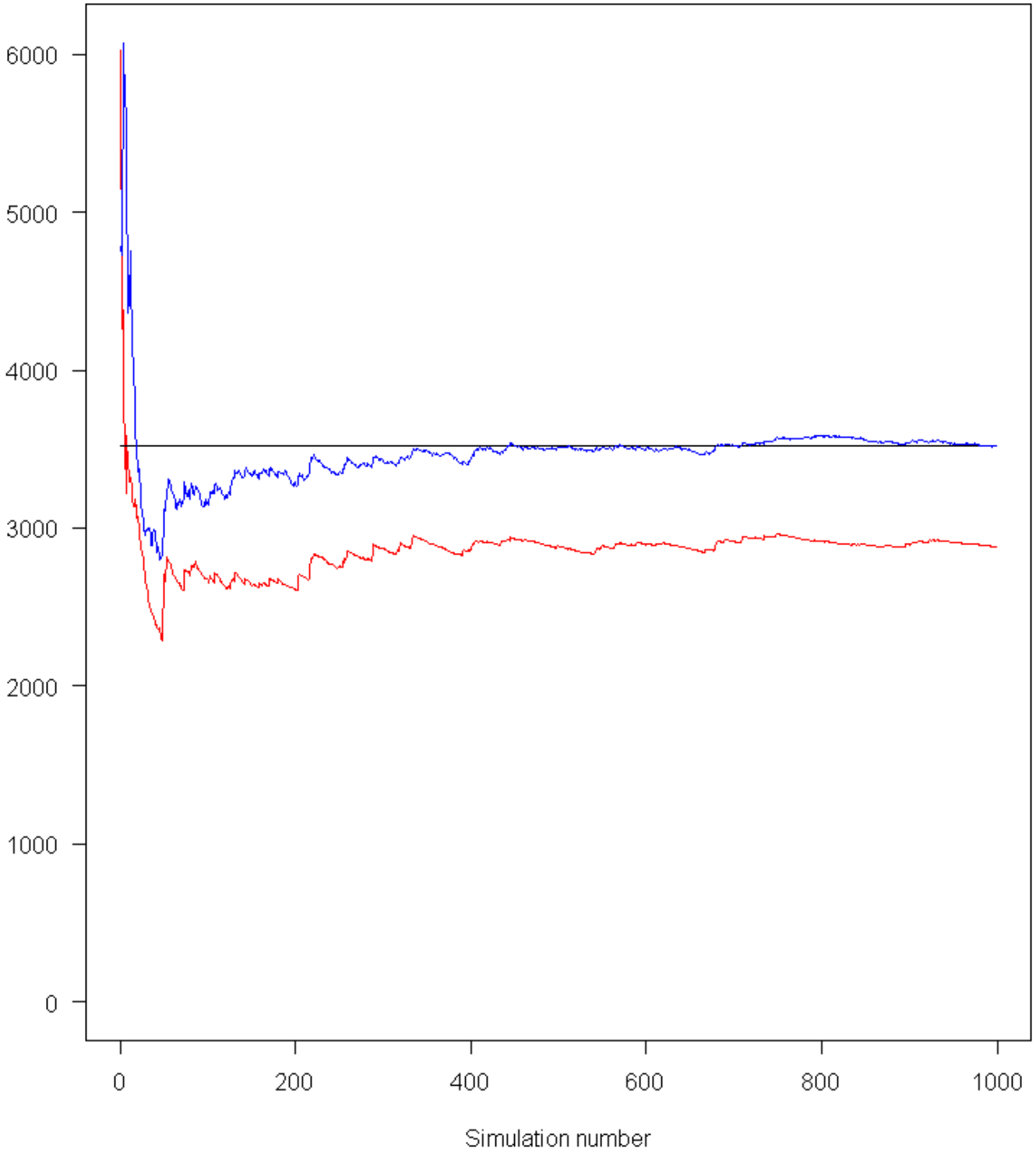

Figure 5.1.: ARL and SRL after simulations.

We assume the situation is stable and in control, however actually we do not know how stable the situation is due to the modification of years without positive donors and the sequential character in the upper control limit. We set up a false alarm probability but the average run length we expect

for the blood donation process to move out of control is not known. Furthermore in the first model the upper control limit is determined by the average rate over all years. The simulation starts with the average over the first 3 years. Working with this average may give rise to some typical unstable scenarios in the start of the simulation.

The bottom line is that there are many situations possible in which the process is assumed to be in control and will nevertheless give a false alarm. As we expect the blood donation process to be in-control in our settings we need to simulate this process for this model enough times.

The average run length (upper line) and standard deviation of the run length (lower line) over 1000 simulations is shown in Figure 5.1. More on the results of this simulation is in Section 6.2.

We now have determined the average run length for one specific realistic scenario with the first model. The average run length for the first model is set to 3519 weeks, which corresponds to approximatly 68 years. This is approximated as the ARL was moving from and towards the line after half of the simulation runs.

The ARL of the second model needs to equal the ARL of the first model for the chosen values of r for the $CCC-r$ chart in order to compare the models in a fair way for example in patterns in the observations. The lower control limits for the second model can be determined analytical such that this will correspond to the same ARL of 3519 weeks. For the $CCC-r$ chart we monitor the blood donation process by using the number of donations with a negative test result before we have r positive donors. We have seen that this number follows the negative binomial distribution which is a generalization of the geometric distribution. For the negative binomial distribution with parameters p and r we know the probability distribution function, see (3.7).

We have the one-sided control chart, the LCL for the negative binomial distribution is calculated in (5.1).

$$\mathrm{F(UCL},r,\, p) = \sum_{i=r}^{LCL} \binom{i-1}{r-1} \cdot p^r \cdot (1-p)^{i-r} = \alpha \tag{5.1}$$

The expected ARL for the $CCC-r$ chart when we set it up with only an LCL is given by (5.2). Note that this ARL is defined as the number of points plotted, hence the number of positive donors, where each point corresponds to r positive donors.

$$\mathrm{ARL}(r) = \frac{1}{1 - \sum_{i=LCL_r}^{\infty} \binom{i-1}{r-1} \cdot p^r \cdot (1-p)^{i-r}} \tag{5.2}$$

We need to equal the ARL of the second model for each r with the ARL of the first model, therefore we work out the expected ARL for the $CCC-r$ charts to the number of time steps in weeks. This is done by calculating the expected number of positive donors in the ARL of the first model, see (5.3).

$$\mathrm{ARL}_2(r) = \frac{\mathrm{ARL}_1 \cdot 1600 \cdot p}{r} \tag{5.3}$$

Substituting the ARL from the first model and combining formulas (5.2) and (5.3) we obtain (5.4).

$$\mathrm{ARL}_1 = \frac{r}{1600 \cdot p} \cdot \frac{1}{1 - \sum_{i=LCL_r}^{\infty} \binom{i-1}{r-1} \cdot p^r \cdot (1-p)^{i-r}} \tag{5.4}$$

The parameters p and ARL_1 are known, therefore we can extract the sum as is done in (5.5).

$$\sum_{i=LCL_r}^{\infty} \binom{i-1}{r-1} \cdot p^r \cdot (1-p)^{i-r} = \frac{(1600 \cdot p \cdot \mathrm{ARL}_1) - r}{1600 \cdot p \cdot \mathrm{ARL}_1} \tag{5.5}$$

The right-hand side can be determined for a specific r. We see that the left-hand side is almost equal to (5.1), hence we can conclude that we are looking for a specific quantile of the negative binomial distribution.

If we substitute the ARL of 3519 and the probability $p = 9.375 \cdot 10^{-5}$ in the right-hand side of (5.5) we have the following quantiles and can set the LCL for each r (see Table 5.3).

r	Needed quantile	LCL	Determined quantile
1	0.981055	2040	0.981057
2	0.962110	32455	0.962112
3	0.943166	92006	0.943167
4	0.924220	168295	0.924222
5	0.905276	255024	0.905276

Table 5.3.: Quantiles and LCL.

These quantiles can not be determined exactly, therefore the value for the LCL that covers at least the value given as the needed quantile, is chosen as the lower control limit. However we can recover the quantile based on the value for the LCL. These quantiles are given in the last column in Table 5.3.

5.3. Procedure for the patterns

As mentioned in Section 4.3, we want to compare the models in some realistic patters. Therefore we can set up some stable situations and start simulating the blood donation process with a change in the input. We have setup two longer situations with 4000 weeks and 88 years where both 60 infections occured with the same assumptions throughout this chapter. The least common multiple of three, four and five is 60, therefore all the $CCC - r$ charts are starting at the same time. The average rate in the first model had time to calibrate and the infections are distributed such that no false alarms are given in the previous 4000 and 4576 weeks, respectively.

We focus on a linear trend and a persistent shift in the indicence rate of a infectious disease, for the simulation of the process that is set by changing the probability per donation that a donor is positive. Three different shifts are simulated and an increase has been set for the trend, however

that takes 10 and 20 years before the increase is finalized. In Table 5.4 and Table 5.5 the numerical change in probability is given.

Shift	p before shift	p after shift
Small (50%)	$9.375 \cdot 10^{-6}$	$1.4063 \cdot 10^{-5}$
Moderate (100%)	$9.375 \cdot 10^{-6}$	$1.8750 \cdot 10^{-5}$
Large (400%)	$9.375 \cdot 10^{-6}$	$3.7500 \cdot 10^{-5}$

Table 5.4.: Design for the persistent shifts.

Trend	p after 5 years	p after 10 years	p after 20 years
Small (50%) in 10 years	$9.375 \cdot 10^{-6}$	$1.4063 \cdot 10^{-5}$	
Moderate (100%) in 10 years	$9.375 \cdot 10^{-6}$	$1.8750 \cdot 10^{-5}$	
Large (200%) in 10 years	$9.375 \cdot 10^{-6}$	$2.8125 \cdot 10^{-5}$	
Small (50%) in 20 years	$9.375 \cdot 10^{-6}$	$1.1719 \cdot 10^{-5}$	$1.4063 \cdot 10^{-5}$
Moderate (100%) in 20 years	$9.375 \cdot 10^{-6}$	$1.4063 \cdot 10^{-5}$	$1.8750 \cdot 10^{-5}$
Large (200%) in 20 years	$9.375 \cdot 10^{-6}$	$1.8750 \cdot 10^{-5}$	$2.8125 \cdot 10^{-5}$

Table 5.5.: Design for the linear trend.

The last situation that has been simulated are with only ten years of donation history. At the start of each simulation a new period of 10 years has been simulated and for each simulation the input was adjusted with the change as given in the tables.

6. Simulation results

Recall that one of the research questions is that we want to know how changes in the incidence rate can best be determined. Simulation runs of the blood donation process were performed to get as many possible situations for the moments a positive donor was found. In this chapter we start with the averages determined after simulations of the run lengths in some stable situations. We performed 1000 simulation runs and we look into some characteristics of those runs. Results on the averages and on the simulation help to interpret the results of the models when we add a change to the process.

We continue with results on the scenarios in the blood donation process when there is a pattern occurring in the incidence rate of a infectious disease. We briefly explain the patterns, the situation the process is in and give results on the simulation of the process. These results on the patterns will be ARL and SRL, but in addition we look closer at the different runs to compare the models and control charts.

6.1. Averages

We have determined the average run length of the process of the first model with annual 83200 whole blood donations done by 52000 donors, see Figure 5.1. There are results for the ARL and SRL under some different settings. We changed the center size and did 1000 simulations to determine the average run length when the size of the center in number of donations is 2.5 times larger. The results on the ARL and SRL are in Table 6.1.

Donations	Donors	Incidence rate	α	ARL	SRL
83.200	52.000	$1.5 \cdot 10^{-5}$	0.05	3519 weeks $\approx$ 68 years	2879 weeks $\approx$ 55 years
208.000	130.000	$1.5 \cdot 10^{-5}$	0.05	3650 weeks $\approx$ 70 years	3163 weeks $\approx$ 61 years

Table 6.1.: Run lengths for whole blood donations.

For this process the average run length had a different kind of behavior compared to the smaller center size. The ARL was for the first 350 simulation runs a lot larger than the average run length of 3650 after 1000 simulations, see Figure 6.1.

The donation type is a setting that can be changed, besides the most common whole blood donation the blood plasma donation is given by plasma donors. They are allowed to come more frequent to donate such that a smaller population will give the same number of donations. This setting has been changed for 83200 and 208000 annual donations respectively. The results for the ARL and SRL are in Table 6.2. This are the averages after 500 simulations of the blood donation process.

The last 2 settings that have been changed, and for which the ARL and SRL have been determined, are the false alarm probability and the incidence rate. Both the false alarm probability and the

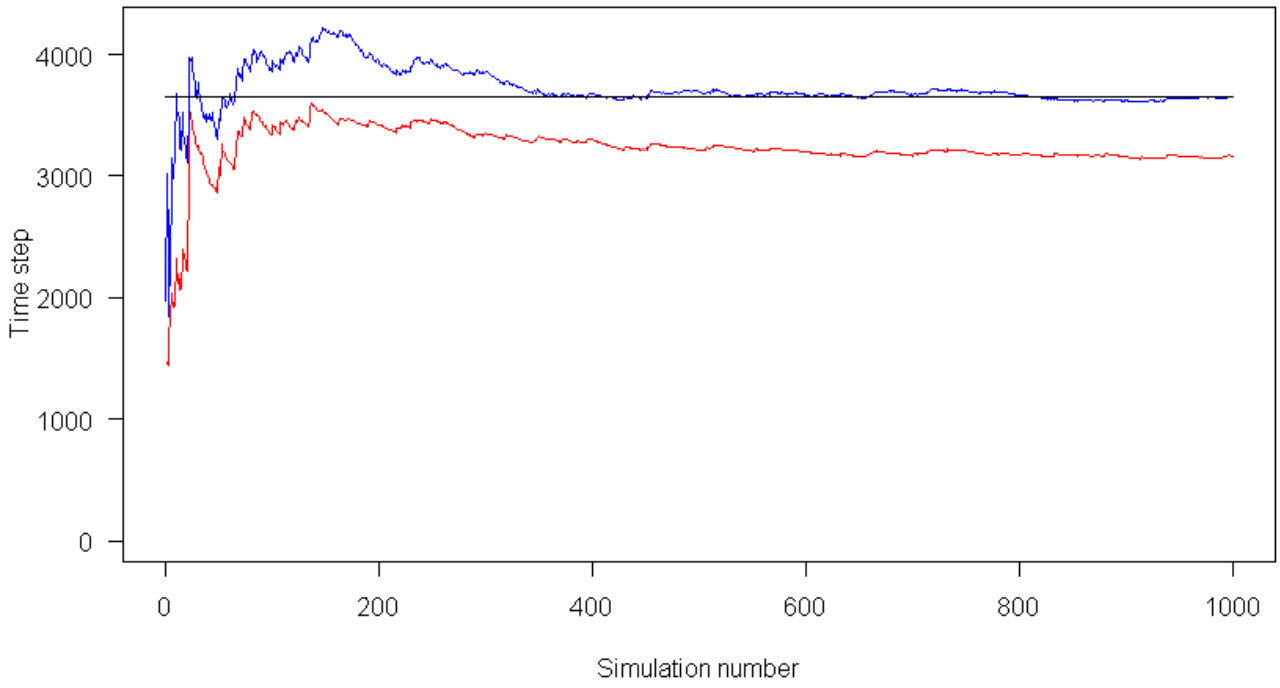

Figure 6.1.: ARL after simulation runs.

Donations	Donors	Incidence rate	α	ARL	SRL
83200	14352	$1.5 \cdot 10^{-5}$	0.05	3597 weeks $\approx$ 69 years	2879 weeks $\approx$ 55 years
208000	35880	$1.5 \cdot 10^{-5}$	0.05	3371 weeks $\approx$ 65 years	2624 weeks $\approx$ 50 years

Table 6.2.: Run lengths for blood plasma donations.

incidence rate are lowered which result in a higher ARL. The averages after 500 simulations are given in Table 6.3.

Donations	Donors	Incidence rate	α	ARL	SRL
83200	14352	$1.5 \cdot 10^{-5}$	0.025	5611 weeks $\approx$ 108 years	4043 weeks $\approx$ 78 years
83200	14352	$0.5 \cdot 10^{-5}$	0.05	5835 weeks $\approx$ 112 years	3726 weeks $\approx$ 72 years

Table 6.3.: Changes in ARL.

6.2. Simulation

The average is determined after making assumptions, see Section 5.1, and simulating the blood donation process 1000 times. One of the assumptions was the maximum amount of years to simulate. We use the simulations with 83200 annual donations given by 52000 donors.

The values of the out of control run length can vary from 1 year up to the maximum set for each simulation of 252 years. Hence a false alarm is given for that specific year as we expect the process

to be in control. The situations in which an alarm is given, can occur when the incidence rate of the donor population for a given year is exceeding the upper control limit. This control limit is established on the average of the previous years, therefore this average is calibrating in the first years on the incidence rate of the previous years. The upper control limit will most likely be exceeded when a certain number of positive donors is found.

In Figure 6.2 we have a situation where there was no alarm given until after 7000 weeks. As the average and UCL were larger for the first 2000 weeks, the observed rate stayed under the upper control limit until that moment after 7000 weeks when the UCL was reduced based on the then current average. Note that the UCL in Figure 6.2 is based on the current average and not on any intermediate result.

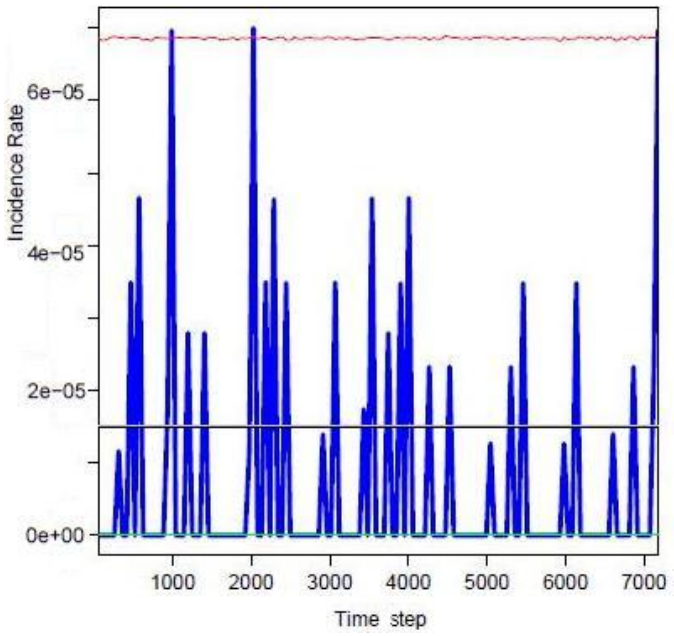

Figure 6.2.: Situation with calibrating average.

Another situation that may occur is that the current average and UCL are less than the average we would expect, see Figure 6.3. In this situation the current average (in gray, lowest straight line) is quite less than the expected incidence rate (in black, line at $1.5 \cdot 10^{-5}$) of the infectious disease.

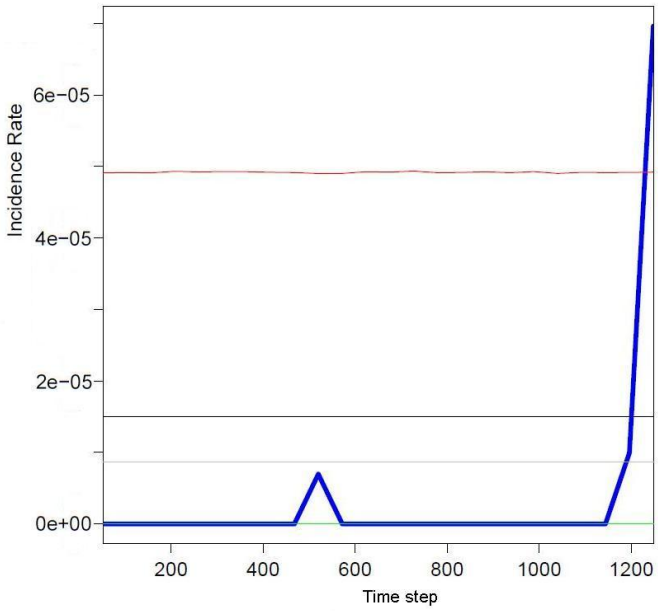

Figure 6.3.: Situation with outburst.

These different situations make that each run length has a different value. We have seen the mean, minimum, maximum and deviation, in addition we can make a histogram to look at the values in more detail. In Figure 6.4 we have the histogram with bins of 200 weeks. Below the ARL of 68 years we have 61% of the runs while 39% of the runs have a length that is higher than the ARL.

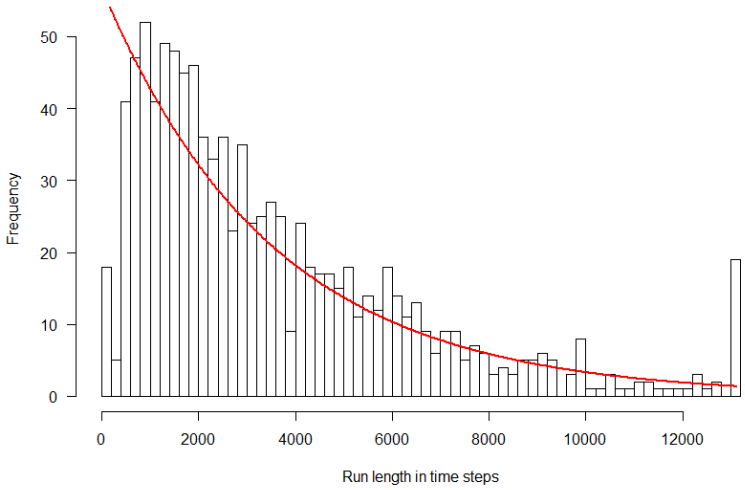

Figure 6.4.: Histogram of the run lengths

We try to fit a geometric distribution on the run lengths of the simulation as we have a Shewhart control chart and since it is known that run lengths are often approximately geometrically distributed (see, e.g. Gold (1989); Chakraborti (2007)). A remark on the fit is that the highest frequency is not found at the first bin(s). The most likely reason is that we have assumed a starting period of 3 years, which allows the average rate and UCL to adjust a bit. In the starting period the total amount of positive donors is low and the upper control limit is adjusted.

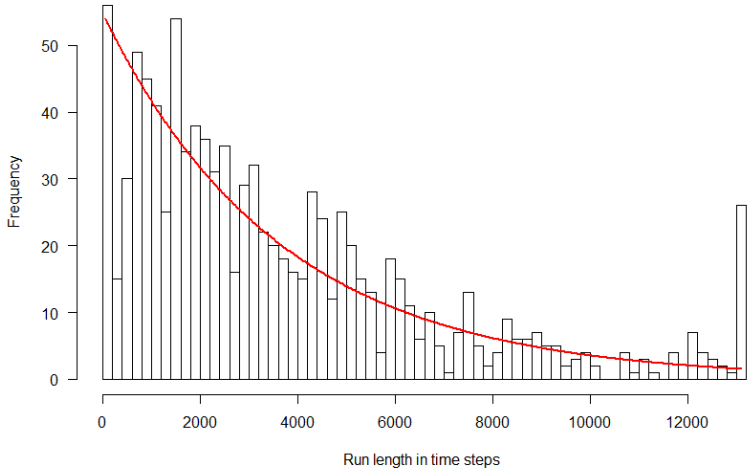

Figure 6.5.: Histogram of the run lengths.

We saw the ARL in Figure 5.1 and in Figure 6.1 have fluctuations. The cause of these fluctuations is the maximum of years that has been set. We are not able to enlarge this maximum in the simulations, however we are able to set a smaller maximum. In Table 6.4 we have an overview on the ARL with a smaller maximum, only 1.9% of the simulation runs has the maximum in our result for the ARL. The calculations on cutting off the simulation at the chosen maximum is correct, see the calculations in Section A.5, as we have seen that the run lengths are approximately geometrically distributed.

Maximal number of years	Number of maximal length runs	ARL
150 years	89	3289 weeks $\approx$ 63 years
175 years	60	3385 weeks $\approx$ 65 years
200 years	38	3446 weeks $\approx$ 66 years
225 years	27	3487 weeks $\approx$ 67 years
250 years	19	3517 weeks $\approx$ 68 years

Table 6.4.: ARL with different maximum.

6.3. Patterns

The patterns in Section 5.3 were simulated 500 times for each pattern with a different setup. The setup contained a number of years with history of the donations. In the first setup we chose to use a fixed history with 60 infections over a period of 88 years. There were no (false) alarms given in these 88 years for both models and all control charts could monitor with a clean history. The period of 88 years was chosen randomly, however the number of infections was chosen as the least common multiple of 2, 3, 4 and 5. Therefore all the $CCC-r$ charts also monitor at the same time.

For each pattern and model the average and standard deviation of the run length before giving an alarm was calculated. In Table 6.5 we have the run lengths on the small patterns, in Table 6.6 on the moderate patterns and in Table 6.7 the run lengths in years on the large patterns. Note that

every $CCC - r$ needs r infected donations before it can give an alarm and the first model is able to give an alarm each year based on the observed and average incidence rate.

	Small shift	Small trend 10 years	Small trend 20 years
Model 1	16.89 (16.49)	21.55 (18.23)	23.53 (17.32)
$CCC - 1$	25.31 (23.85)	29.53 (24.93)	31.48 (25.03)
$CCC - 2$	23.31 (22.03)	26.00 (21.41)	29.01 (21.05)
$CCC - 3$	21.23 (19.70)	23.42 (18.50)	27.33 (20.19)
$CCC - 4$	18.15 (15.32)	23.15 (17.57)	25.26 (17.03)
$CCC - 5$	17.23 (14.50)	22.34 (16.26)	25.70 (16.85)

Table 6.5.: ARL (SRL) detecting patterns after 88 stable years.

	Moderate shift	Moderate trend 10 years	Moderate trend 20 years
Model 1	8.93 (9.31)	11.18 (6.58)	16.76 (10.51)
$CCC - 1$	16.72 (17.18)	18.30 (15.41)	21.41 (16.21)
$CCC - 2$	11.85 (11.12)	14.47 (10.54)	19.97 (12.29)
$CCC - 3$	9.95 (8.75)	12.89 (8.64)	17.28 (9.10)
$CCC - 4$	9.28 (7.66)	12.64 (7.81)	16.88 (8.23)
$CCC - 5$	8.67 (6.34)	11.86 (6.12)	17.03 (7.84)

Table 6.6.: ARL (SRL) detecting patterns after 88 stable years.

	Large shift	Large trend 10 years	Large trend 20 years
Model 1	2.42 (1.09)	7.41 (3.43)	11.01 (5.20)
$CCC - 1$	3.87 (4.00)	11.25 (7.24)	15.01 (8.89)
$CCC - 2$	2.61 (2.18)	8.92 (4.43)	12.72 (6.37)
$CCC - 3$	2.47 (1.54)	8.04 (3.73)	11.77 (5.15)
$CCC - 4$	2.67 (1.50)	8.07 (3.03)	11.76 (4.50)
$CCC - 5$	2.32 (1.57)	8.16 (2.73)	11.62 (4.46)

Table 6.7.: ARL (SRL) detecting patterns after 88 stable years.

The lowest ARL for most of the patterns is given by the first model, in some situations closely followed by the $CCC - 3$, $CCC - 4$ and $CCC - 5$ control charts from the second model. If we take a closer look to the SRL we see that the $CCC - r$ control charts have less standard deviation in their run lengths. However that is not the case with the $CCC - 1$ and $CCC - 2$ control chart, these charts do not seem to be able to notice the patterns in a stable way such that the ARL and SRL are both smaller.

If there was no alarm given in a specific simulation for a model, a maximum of 192 years was set. In Table 6.8 are the occurrences of the situations without an alarm. The first model was able to give an alarm for the change in the system in all of the simulation runs.

The period of 88 years is sufficiently long for the average rate in the first model to be calibrated. In Table 6.9 we present the percentage of the simulation runs that a specific model was the first to detect the pattern. The percentages are adjusted to the total since the $CCC - r$ charts are able to give an alarm at the same infection.

	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	2,6%	1,8%	1%	0,2%	0,2%
Moderate shift	0,6%	-	-	-	-
Large shift	-	-	-	-	-
Small trend 10 years	3%	1,2%	0,2%	0,2%	0,4%
Small trend 20 years	2,2%	1,2%	1%	0,4%	0,2%
Moderate trend 10 years	-	-	-	-	-
Moderate trend 20 years	0,4%	-	-	-	-
Large trend 10 years	-	-	-	-	-
Large trend 20 years	-	-	-	-	-

Table 6.8.: No alarm given.

	First model	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	8.1%	24.6%	20.9%	15.7%	17.0%	13.6%
Moderate shift	9.4%	21.6%	23.4%	16.9%	15.7%	13.0%
Large shift	6.6%	28.5%	27.1%	8.6%	10.9%	18.4%
Small trend 10 years	5.7%	26.7%	23.2%	18.7%	13.3%	12.4%
Small trend 20 years	7.0%	27.4%	21.3%	16.6%	14.8%	13.0%
Moderate trend 10 years	10.7%	27.6%	22.0%	13.7%	15.1%	10.9%
Moderate trend 20 years	6.1%	26.8%	21.6%	17.0%	16.3%	12.1%
Large trend 10 years	6.6%	23.0%	22.2%	20.8%	16.7%	10.7%
Large trend 20 years	6.4%	25.0%	23.0%	16.2%	15.2%	14.1%

Table 6.9.: First alarm given.

In Figure 6.6 we have the cumulative distribution of the run lengths for each control chart after a moderate trend was inserted after 10 years. We see that the $CCC-5$ control chart has a similar pattern as the chart of the first model. The $CCC-3$ and $CCC-4$ show a similar line and it is clear that the $CCC-1$ chart has quite a different distribution function.

Either the number of infections or the number of years is not what we would expect in the setup with 88 years. We actually expect 60 infections in a period of 4000 weeks. The simulations for this setup showed similar results as the previous setup. These results can be found in Section A.6.

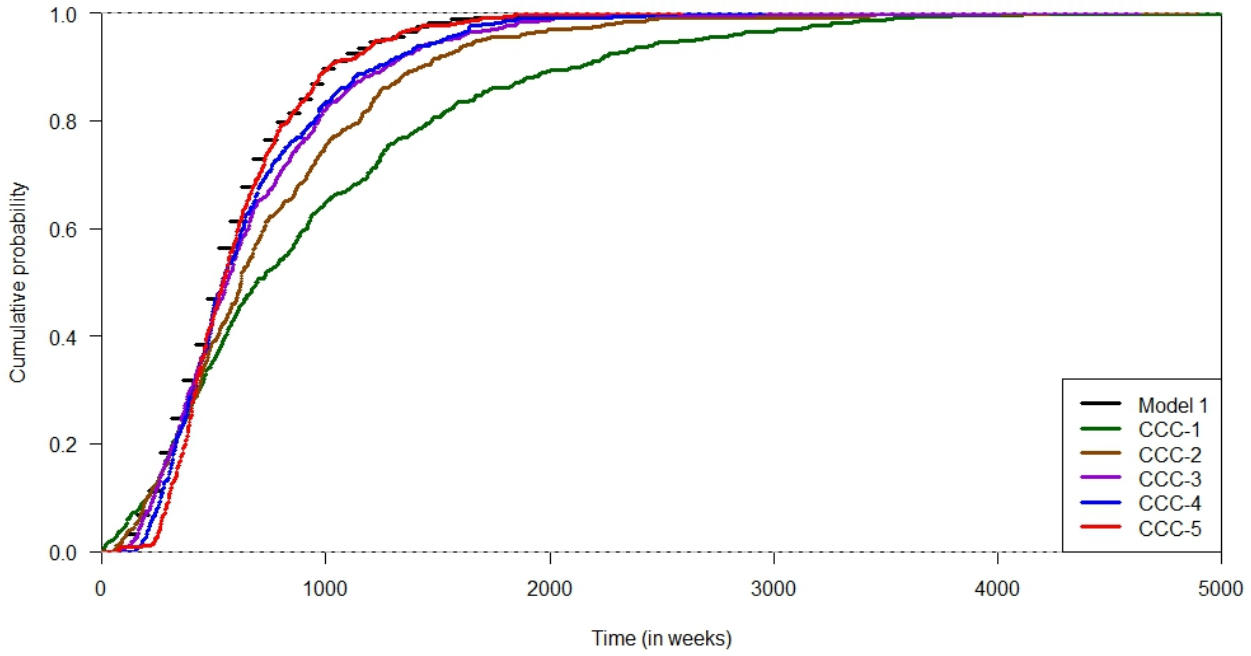

Figure 6.6.: Cumulative distribution of run lengths after moderate trend in 10 years.

For the last setup we generated 10 years of donation history and that gives a wide range of the number of infections. The $CCC-r$ charts will count the conforming donations where, most likely, a number of non-conforming donations was included. As the first model makes use of the observed incidence rate it is highly dependable on the generated number of donations and infections in the period of 10 years. For that reason the focus of the simulation where 10 random years were generated was on the trends. In Table 6.10 and in Table 6.11 we have the ARL and SRL from the simulation with the trend fulfilled after respectively 10 and 20 years. In Table 6.12 we have the ARL and SRL for the shifts after that 10 generated years.

	Small trend 10 years	Moderate trend 10 years	Large trend 10 years
Model 1	28.03 years (27.05)	15.81 years (15.60)	11.33 years (10.31)
$CCC-1$	32.18 years (27.78)	19.20 years (17.58)	10.87 years (7.93)
$CCC-2$	27.95 years (24.44)	14.20 years (10.02)	8.01 years (4.66)
$CCC-3$	24.03 years (20.93)	12.61 years (8.06)	7.27 years (3.89)
$CCC-4$	21.67 years (18.16)	12.23 years (7.32)	6.75 years (3.48)
$CCC-5$	21.25 years (17.96)	11.88 years (6.58)	6.69 years (3.09)

Table 6.10.: ARL (SRL) detecting patterns after 10 year of donations.

	Small trend 20 years	Moderate trend 20 years	Large trend 20 years
Model 1	26.96 years (23.83)	21.61 years (19.52)	14.86 years (11.15)
$CCC-1$	29.56 years (24.95)	17.92 years (16.57)	14.39 years (8.69)
$CCC-2$	28.96 years (23.46)	15.31 years (13.86)	12.32 years (6.28)
$CCC-3$	24.45 years (18.03)	13.57 years (11.61)	11.01 years (5.56)
$CCC-4$	22.95 years (16.86)	12.67 years (10.05)	10.21 years (5.01)
$CCC-5$	20.91 years (15.00)	12.85 years (9.68)	10.43 years (4.99)

Table 6.11.: ARL (SRL) detecting patterns after 10 year of donations.

	Small shift	Moderate shift	Large shift
Model 1	25.38 years (26.49)	17.64 years (22.30)	3.87 years (4.95)
$CCC-1$	23.28 years (22.27)	14.21 years (14.13)	4.23 years (3.89)
$CCC-2$	22.31 years (20.92)	10.70 years (10.74)	2.45 years (2.26)
$CCC-3$	17.92 years (16.24)	8.43 years (7.81)	2.05 years (1.64)
$CCC-4$	17.75 years (16.83)	7.28 years (6.30)	2.02 years (1.38)
$CCC-5$	14.66 years (13.02)	7.30 years (5.73)	2.31 years (1.40)

Table 6.12.: ARL (SRL) detecting patterns after 10 year of donations.

We have quiet remarkable results as it seems that the ARL and SRL for the first model are really exceeding the ARL and SRL for almost all $CCC-r$ control charts. The first model does still have a low ARL for the small and moderate trends however there is much fluctuation for all other patterns. Based on the ARL in combination with the SRL it shows that the $CCC-4$ and $CCC-5$ control charts have the lowest ARL for the out-of-control situation, closely followed by the $CCC-3$ control chart.

For all patterns the simulation consisted of a minimal of 500 runs and with some of the runs a few control charts did not pick up the trend in the incidence rate, Table 6.13.

	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	1.0%	0.6%	0.2%	0.4%	-
Moderate shift	-	0.2%	-	-	-
Large shift	-	-	-	-	-
Small trend 10 years	4.0%	2.2%	1.0%	0.8%	0.2%
Small trend 20 years	2.0%	1.8%	-	-	0.2%
Moderate trend 10 years	0.4%	-	-	-	-
Moderate trend 20 years	0.2%	-	0.2%	-	-
Large trend 10 years	-	-	-	-	-
Large trend 20 years	-	-	-	-	-

Table 6.13.: No alarm given for the trends after 10 years generated donations.

Each time that the observations after the first 10 went outside the control limits an alarm was given for either any control chart. The first alarms given by each control chart were counted and scaled to 100%. In Table 6.14 we have the percentages. We can see some differences with the other setups as the charts from the second model do not start the counting of conforming donations at the same time step.

	First model	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	10.7%	23.2%	19.0%	15.1%	14.1%	17.9%
Moderate shift	6.3%	18.9%	19.9%	18.9%	18.0%	18.0%
Large shift	2.8%	16.2%	25.7%	23.7%	18.5%	13.1%
Small trend 10 years	11.0%	20.9%	18.5%	19.5%	15.3%	14.8%
Small trend 20 years	13.7%	22.8%	17.2%	14.8%	16.2%	15.4%
Moderate trend 10 years	10.8%	20.9%	21.1%	18.0%	13.2%	15.9%
Moderate trend 20 years	5.0%	20.8%	20.7%	18.3%	18.3%	16.9%
Large trend 10 years	7.7%	18.7%	19.9%	19.8%	15.1%	18.7%
Large trend 20 years	8.6%	21.2%	18.1%	19.0%	17.6%	15.4%

Table 6.14.: First alarm given.

In Figure 6.7 we see the cumulative distribution of the control charts of the run lengths of the moderate trend after 10 years.

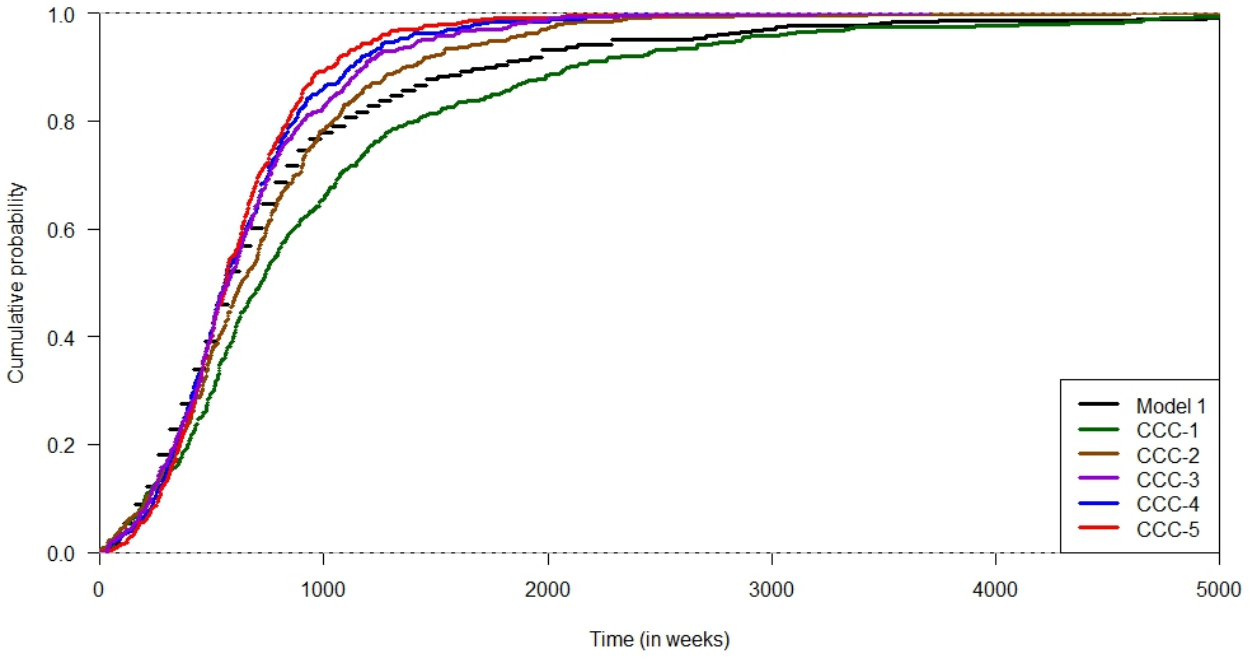

Figure 6.7.: Cumulative distribution for the run lengths moderate trend after 10 years.

7. Conclusions

The conclusions are divided into conclusions on the blood donation process and on the results of the simulations where we compare the monitoring strategies. We answer our research questions from the introduction in Chapter 1.

7.1. Blood donation process

The blood donation process is a process where donors are the manufacturers of the product, the blood donation. The defects in this blood donation process are those donors that are tested positive for a infectious disease. The products from positive donors have to be destroyed and the donor can not manufacture products anymore. The donors have restriction on the amount of products and are prior to their production screened on a list of risk factors.

For each individual defect or positive donor the cause is being determined. All defects are recorded and these need to be monitored on a higher level. The current monitoring strategy is based on a model that sets the numbers after a certain time step. For the authorities this time step is one year. The annual reports contain the numbers of positive donors and numbers on the donor populations.

A Shewhart control chart monitors the observed incidence rate of each infectious disease for the first time donor and for the repeat donor population. The incidence rate is determined on the donor and their frequency of donations. The observed rate and the control limits are constructed assuming the incidence rate of a infectious disease is Poisson distributed.

These incidence rates are being tested, the guideline states that the incidence rate of the current year should be tested against the incidence rates of the three years prior to the current year.

In addition on the process there are many individual blood/plasma collection centers or more commonly used regions. The guideline for the regions is to test for differences across the regions in the incidence rate for the current year. These guidelines do not allow us to pick up slower trends.

A new approach to monitor the positive donors in the blood donation process is introduced as it can be helpful to fit the incidence rate of each infectious disease, which was one of the research questions. The model focuses on the number of donations without positive donors. The model counts the conforming donations between one or more infections. This model is more commonly used in zero-defect processes, the blood donation process is one of those processes. For this model the distribution of the occurrence of one defect is assumed to have a Geometric distribution. If the donations in between more defects are counted we assume a Negative Binomial distribution for the number of donations. For this model $CCC-r$ charts can be given with the desired control limits.

7.2. Comparison of monitoring strategies

To give a decent answer to the research questions in the introduction the blood donation process has been designed in the form of a simulation where a variety of settings could be customized to establish desired scenarios. Both models have been implemented in the simulation and in order to determine differences in the models, the models had to be made comparable. The performance measure, the ARL, of both models had to be equalized. This leads to the following steps to be able to use the models and make the simulations comparable:

- Run the simulation with the first model 1000 times (or more) with the desired settings on false alarm probability and upper control limit.
- Determine the ARL, average run length, based on the run lengths where an false alarm is given on the first model.
- Substitute the ARL from the first model in the formula for the ARL of the second model.
- Calculate the corresponding lower control limits for each chart by determining the quantiles of the negative binomial distribution.

The performance measures ARL and SRL have been determined under different settings by simulations. For different blood/plasma collection centers the measures were compared. Size of the center and the donation frequency of the donor population were changed, however the ARL and SRL seemed quite comparable.

The models are compared with different scenario's and with certain changes on the incidence rate. The sudden persistent shifts and the slower linear trends changed the incidence rate for the donor population in the first model or the probability a defect was found at a donation in the second model.

Based on the simulations on the performance measures ARL and SRL the following conclusions can be made on the models for a longer pre-determined period :

- Small changes, the first model has the smallest out-of-control ARL. However the CCC charts with $r = \{3, 4, 5\}$ give very comparable or even better results in combination with the SRL.
- Moderate changes, based on the ARL in combination with the SRL we should prefer the CCC charts with $r = \{3, 4, 5\}$ over the first model as the SRL for the first model is larger than the SRL's for the second model while the ARL is comparable.
- Large changes, the first model performs best for the large shift, however for the large trends the ARL/SRL of the second model is comparable with the first model for $r = \{3, 4, 5\}$.
- Based on ARL and SRL the first model and the second model with $r = \{3, 4, 5\}$ are almost equal. The control charts of the second model with $r = \{1, 2\}$ give poor results on the ARL and SRL.

Besides the ARL and SRL we have seen the amount of runs in which no alarm was given or which model gives the first alarm. We see a wide range of percentages for the first alarm that is given, however it seems clear that an annual model is always slower than an on-going model. The second model does have some trouble finding a smaller change in the simulation in the maximal number of time steps. However if we determine if the first model or a chart from the second model is able to detect the change in a specific year first we notice that the second model is first to detect more often.

In addition a period of 10 years with donations was generated, which might be more realistic over the longer period as at the moment most countries have correct and detailed numbers for the last 10 years. In this period of 10 years (and after) the first model is still calibrating the average rate. We conclude on the results for this period:

- Linear trend established after 20 years, based on the ARL we see that the $CCC-r$ control charts are able to notice the moderate and large trend before it has reached its value after 20 years. The smaller trend seems more difficult to detect beforehand. The indication we get from the SRL is that the $CCC-r$ control charts with $r=\{3,4,5\}$ have a low SRL, while for the first model and the charts with $r=\{1,2\}$ the SRL comes close to the ARL.
- Linear trend established after 10 years, as for the trend established after 20 years the results for the control charts are about the same. Expect that the values for both ARL and SRL are smaller as the incidence rate is increasing sooner.
- Persistent shift, for the small, moderate and large shift we have almost identical results. The $CCC-r$ control charts with $r=\{3,4,5\}$ have the lowest ARL and SRL. The $CCC-r$ control charts with $r=\{1,2\}$ are performing even better than the control chart for the first model, however the high SRL indicates the charts are not that stable in detecting the patterns in all the simulation runs.
- For the first model it is more difficult to detect the patterns while working with the observed average rate of 10 years. As seen for the longer pre-determined period the first alarm is most often given by any of the $CCC-r$ control charts. Due to the 10 years of generated donations the $CCC-r$ are not starting at the same time therefore the $CCC-r$ control charts with $r=\{3,4,5\}$ are able to detect the patterns earlier. For $r=\{3,4,5\}$ the charts give more often the first alarm such that the second model is quicker to detect the pattern in the first year on a large amount of simulation runs.

The first model is able to adequately monitor the process, but so does the second model. Monitoring the process can benefit with the addition of the second model. A monitoring system based on the count of conforming donations can make it easier to monitor the blood donation process on the level of the individual blood/plasma collection center, on a regional level or on a national level.

The indications on the detection of change in the incidence rate from the simulations give a preference for the combined charts of the second model over the control chart of the model that is used nowadays. The second model is able to detect the changes sooner than the first model not only because the positive donors are found during the year, but also in a earlier time step.

The ARL is quite a flawed measure for detecting the patterns. Some charts from the second model were not able to detect the pattern at all which resulted in high ARL and SRL. However other charts gave similar results for the ARL and SRL with the first model.

It seems clear that monitoring the donations is a good alternative besides the annual incidence rate. Monitoring the infections in the blood donations relates to an overlap of more annual reports, which surely can not be said to be a bad thing.

7.3. Research questions

We have constructed the framework to compare two models and their monitoring strategies. The current monitoring guidelines are based on the incidence rate of a donor population for a given time step. This time step is chosen as one year as reports on (positive) donors needs to be reported annually. Another model can be used to monitor the incidence rate of particular infectious diseases (HBV, HIV and HCV) by determining the probability a donation is given by a positive donor. Counting the number of conforming donations has advantages over the annual reports. This model can be a better fit for monitoring as it is more common to be used in zero-defect processes. The model is able to count and monitor the number of donation in between more than 1 infection and it is known to have less false alarms.

The models were implemented in a simulation program which allowed us to generate the blood donation process. Settings such as the size of the blood/plasma collection center and the type of donation could be changed. The average run length and standard deviation of the run lengths are the measures of the performance. The results on this measures while we change the size of the center and the donation type show slight variability. However in terms of years the ARL does not seem to differ that much. The small differences in the ARL are due to higher odds that with more donation or donors in a certain year. This is more often seen when the run lengths are geometrically distributed.

With the framework to compare both models, changes in the incidence rate could be determined. Sudden persistent shifts and linear trends were implemented to change the incidence rate of a infectious disease in different scenarios. In conclusion both models are able to adequately monitor the process and are able to detect changes in the process, but there are differences. In most of the simulated situations one of the control charts of the second model will be first to detect the change, also on a annual basis. Although it might be difficult in some situations to detect the change the ARL/SRL of one of the charts of the second model seems more stable than the ARL/SRL from the first model. In particular when 10 years of the blood donation process was generated the control charts of the second model showed much better results than the first model.

The ARL has shortcomings as performance measure, but in combination with the SRL the indication for which model to use to detect changes in the incidence rate gives a clear direction. The second model demonstrates its strength in many situations. Specific for the control charts of the second model, the $CCC - r$ charts with $r = \{3, 4, 5\}$ show better results on the ARL and SRL while the $CCC - r$ charts with $r = \{1, 2\}$ have better results on being first to detect the changes in the process. As the first model gives a annual and decent global overview on the donor population, the second model shows any change in the system. If no more positive donors are found for a particular infectious disease over a longer period the second model will count the number of donations between the infections and the first model counts the donor years of the donor population. The optimal strategy for the detection of smaller patterns does not seem to have a large preference in one of the models.

8. Recommendations

In this chapter we will give recommendations on two aspects, namely for future research and for the guidelines. For the future research we go into detail for the simulation and the parts that were not researched. The simulation allows the user to change many settings and input to generate the blood donation process. On these settings the performance measures ARL and SRL can be determined. Topics that can be considered for further depth have been documented throughout this research. Some links related to this research have yet to be made. Furthermore we mention recommendations on the current monitoring technique, which is in use in the guidelines set by the EMA, and we have suggestions for Sanquin.

8.1. Future research

The tests that are currently in use and performed in Chapter 2 are merely looking at the differences in either the incidence rate over years or the differences across regions in one specific year. The guidelines on the testing methods have been expanded by enlarging the historical data in the tests. However we did not set up the hypothesis to test for the moment a change entered in the system, see (3.9). Furthermore the link between the control charts used in Chapter 2 and the testing methods have not been fully established yet. For the prevalence rate, which was described in Chapter 2, the testing methods as done for the incidence rate can not be done in the same way and as for now there are no strategies yet. Actually, for the prevalence rate, the monitoring strategy is not performed in the simulation as it is simply a higher rate than the incidence rate.

Ideally, a good control chart should have an appropriately high ARL when the process is in control and an appropriately low ARL when the process is out of control. However the ARL has shortcomings. Diverse literature give indications that it should be used in combination with other performance measures. In combination with the SRL the ARL is able to give a better indication, although in the set up of the simulation the ARL is influenced by setting maximums or by false alarms.

In the histograms, (Figure 6.4) and (Figure 6.5) we see that the results of the run lengths in Chapter 6 do not entirely give the expected distribution. We could consider performing even more simulations to make the run length distribution smoother. The same holds for the maximal time step we have set for the process, by setting this maximal time step the distribution of the run length as a result of the simulations is not smooth.

The control charts of the second model, the $CCC - r$ charts, are all being used on the donations, since the donors have a recurring pattern with a certain frequency each year. By this assumption the donor population is generalized. The frequency of the different donors and their donation type can be determined quite exactly, however the number of donor years, used in the current guidelines for monitoring, can possibly change the monitoring strategy. This other set up could be part of future research.

Some decisions were made on what to research. Spatial statistics were mentioned in the beginning, but did not take a part in the research. The exact localization of the non-conforming infections could be researched. This was not chosen since the donor population is constantly moving and is allowed to make their donation at any center that is appropriate at that time for the donor. We do however see that this does not happen often.

Diverse settings in the first model and settings for the second model can be changed. Average run lengths were determined with different settings for the sizes of the centers, but not all details and changes in the process were adapted to all those settings. Besides the sizes of the center, we could make the frequencies of the donor population, the false alarm probability and different incidence rates part of future research. The results in Chapter 6 do give clear indications of what to expect.

In Chapter 3 we mentioned two other control charts, namely the CUSUM and the EMWA control chart. It is known from literature that these control charts are able to pick up (persistent) shifts and trends quicker than the Shewhart control charts. Part of determining if the process is out-of-control is setting hypotheses. For example we can test the process for a persistent change of the mean or for an epidemic pattern, Di Bucchianico et al. (2004). Setting up different hypotheses and testing them in combination with the simulation could be part of further research. As we saw some hypotheses in Chapter 2, these can also be compared to be even more sure about the strength or lack of strength in the detection of persistent shifts or slow trends. The focus in this thesis was on the two models and their two type of control charts. However the other control charts and tests can complete the impact of new strategies in the blood donation process.

8.2. Guidelines EMA and Sanquin

In the guidelines for the EMA the incidence rate of a donor population is established by the donor years. The calculation for the number of donor years is approximated as it is not certain what the donation interval is for each donor individually. There are many different donors in the donor population and each donor will donate a numerous times based on the type of donation as the donor is called to make a donation. Furthermore the number of times a donor donates in a particular year can vary from 0 up to 23 times, because there is a increased need for some specific blood group. The different type of donors and type of donations need to be monitored which is currently done with the donor years. Monitoring the donations given by the donor population is quite a different approach. One can argue whether monitoring donor years or monitoring donations is easier to use or is one of them can be stricter for the process.

Every donor that is tested positive for any infectious disease gets an evaluation to determine the cause of the infection and perhaps additional risk factors. The individual approach on all donors and infections is needed to address upcoming issues. The bigger picture is to monitor all of the infections and positive donors over a longer period. The questions for that longer period are what type of change to detect and what time frame is acceptable to detect the change. Also the aggregation level of the change (e.g., at regional level or at individual center level) needs to be specified. With many donations and a small amount of positive donors we need to know if there is in fact anything to detect and over which period we want to do this. From literature and by establishing a framework to look into details we know that the current monitoring guidelines can be improved and that those improvements can be established in a better way than setting thresholds on (particular) individual centers or regions. Therefore we highly recommend to add the $CCC - r$ control charts in the monitoring strategies for infectious diseases in the blood donation process.

The mathematical approach given throughout this thesis for monitoring infectious diseases in the blood donation process gives many new insights and is able to establish improvements on the current monitoring strategies for now and in the long run.

A. Appendix

A.1. HBV, HIV and HCV

This general information on the three infectious diseases (hepatitis B, HIV, and hepatitis C) are summarized from the website of the Center for Disease Control and Prevention (CDC) US Government.

Hepatitis B is caused by infection with the hepatitis B virus (HBV) and the incubation period from the time of exposure to onset of symptoms is 6 weeks to 6 months. HBV is found in highest concentration in blood and in lower concentrations in other body fluids. The HBV infection can be self-limited or chronic. The risk for chronic infection is related to the age at infection, approximately 90% of infected infants and 30% of infected children aged younger than five years become chronically infected, compared with 2% to 6% of adults. If a person has a chronic HBV infections, the risk for premature death from cirrhosis or hepatocellular carcinoma is 15% to 25%. Primary risk factors that have been associated with infection are unprotected sex with an infected partner, birth to an infected mother, unprotected sex with more than one partner, men who have sex with other men, history of other sexual transmittable diseases and illegal injection drug use. It is possible to receive vaccination for hepatitis B in order to prevent the disease.

The human immunodeficiency virus (HIV) is the virus that can lead to acquired immunodeficiency syndrome. Once a person has HIV infection, the person cannot get rid of the virus. A chimpanzee in West Africa has been identified as the source of HIV infection in humans. The virus was most likely transmitted to humans and the virus later slowly spread across Africa and into other parts of the world. HIV affects specific cells of the immune system and over time these cells can be destroyed such that the human body can not fight off infections and other diseases, then the virus can then lead to AIDS.

With proper medical care, viral replication can be controlled. People infected with the virus can get treatment which also lowers their chance of infecting others. Untreated infection is almost universally fatal since it overwhelms the immune system. Treatment can help people at all stages of the disease though. Within two to four weeks after infection with HIV, flu symptoms may occur. Large amounts of the virus are produced in a persons body. The ability to spread HIV is highest during this stage, but eventually the amounts are falling back to a stable level. It is also possible that the infection has a different phase. The clinical latency is the period sometimes called asymptomatic HIV infection or chronic HIV infection. During this phase, HIV is still active, but reproduces at very low levels. The symptoms may not occur and people that are on antiretroviral therapy may live with clinical latency for several decades. For people who are not on this therapy, this period can last up to a decade, but some may progress through this phase faster. The person is still able to transmit the infection, however the therapy reduces this risk. Towards the middle and the end of the clinical latency period your immune system will be weakened by the infection.

In the AIDS stage of the infection the immune system is badly damaged and the body is very vulnerable to infections and infection-related cancers. Without treatment, people who are diagnosed with AIDS typically survive about 3 years.

Hepatitis C virus (HCV) is most efficiently transmitted through large or an repeated exposure to infected blood, that can be through transfusion of blood from unscreened donors or through use of injecting drugs. Less frequent are occupational, perinatal, and sexual exposures but those can also result in transmission of HCV. Sixty to 70% of persons newly infected with HCV typically are usually asymptomatic or have a mild clinical illness. The virus can be detected in blood within one to three weeks after exposure. The average time from exposure to HCV antibody (anti-HCV) seroconversion is eight to nine weeks, and anti-HCV can be detected in over 97% of the persons by six months after exposure. Chronic HCV infection develops in 70 to 85% of HCV-infected persons and 60 to 70% of chronically infected persons have evidence of active liver disease. The majority of infected persons might not be aware of their infection because they are not clinically ill. However, infected persons serve as a source of transmission to others and are at risk for chronic liver disease or other HCV-related chronic diseases decades after infection.

A.2. Results likelihood ratio test

In this section the results from the sequential testing method (see Section 2.2) from HIV in Table A.1 and from HCV in Table A.2 are given.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	0.0883	**0.0206**	0.2026	0.5005	0.437	0.8093	0.4378	0.5754	0.6006	0.4741	0.1233
Two previous years		0.0613	0.8990	0.8710	0.5921	0.8734	0.2463	0.8913	0.8338	0.1808	0.3998
Three previous years			0.8908	0.3457	0.3389	0.9742	0.3200	0.9243	0.5854	0.2251	0.5500
Four previous years				0.4407	0.7613	0.7336	0.2674	0.9892	0.4541	0.1442	0.5273
Five previous years					0.6434	0.9481	0.3692	0.9517	0.4950	0.0979	0.6186
Six previous years						0.9901	0.2089	0.9371	0.4278	0.0992	0.7878
Seven previous years							0.2407	0.8197	0.5296	0.0852	0.7868
Eight previous years								0.8624	0.3506	0.1079	0.8583
Nine previous years									0.3679	0.0668	0.7695
Ten previous years										0.0716	0.9773
Eleven previous years											0.9578

Table A.1.: p-values sequential testing HIV IR Netherlands 2001 to 2012

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	0.3444	0.0883	0.0547	0.4355	0.1055	0.1528	0.4822	0	0	0	0
Two previous years		0.1394	0.4045	0.8400	0.1536	0.3510	0.0539	0.5172	0	0	0
Three previous years			0.3288	0.5809	0.0501	0.3408	0.0851	0.1413	0.5979	0	0
Four previous years				0.7157	0.0931	0.5354	0.0762	0.1674	0.1877	0.6044	0
Five previous years					**0.0403**	0.4939	0.1260	0.1458	0.1996	0.2328	0.6277
Six previous years						0.6078	0.1076	0.1959	0.1634	0.2634	0.3086
Seven previous years							0.1262	0.1691	0.2130	0.2137	0.3002
Eight previous years								0.1939	0.1915	0.2451	0.2422
Nine previous years									0.2102	0.2188	0.2934
Ten previous years										0.2287	0.2449
Eleven previous years											0.2591

Table A.2.: p-values sequential testing HCV IR Netherlands 2001 to 2012

A.3. Results regional testing

In this section the results from the regional testing method (see Section 2.2) from HIV in Table A.3 and from HCV in Table A.4 are given.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	**0.0330**	0.7027	0.0518	0.2027	0.1052	0.4602	0.4930	0.7385	0.1335	0.7362	0.3348
Two previous years		0.5639	0.471	0.1927	0.3272	0.8835	0.4347	1.0000	0.4099	0.4888	1.0000
Three previous years			0.1817	0.5574	0.4636	0.6917	1.0000	0.7735	0.7065	0.4756	0.4202
Four previous years				0.1580	0.7429	0.3162	0.8970	0.8993	0.5897	0.7029	0.1632
Five previous years					0.2921	0.5841	0.5860	0.7287	0.7882	0.5887	0.4261
Six previous years						0.1602	0.7805	0.4742	0.5560	0.8041	0.5470
Seven previous years							0.3183	0.6890	0.3226	0.5708	0.5851
Eight previous years								0.2486	0.4993	0.3262	0.3616
Nine previous years									0.1619	0.5179	0.2364
Ten previous years										0.1665	0.3955
Eleven previous years											0.1229

Table A.3.: Regional tests for HIV with data from previous years.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
One previous year	0.1611	0.2610	0.0631	0.5183	0.7558	0.7358	1.0000	0	0	0	0
Two previous years		0.2537	0.5105	0.6502	0.7708	0.8650	0.7349	0	0	0	0
Three previous years			1.0000	0.6534	0.8014	0.8828	0.8652	1.0000	0	0	0
Four previous years				0.9570	0.7975	0.9726	0.8887	0.9078	1.0000	0	0
Five previous years					1.0000	0.9753	0.9738	0.8879	0.8165	1.0000	0
Six previous years						0.9807	0.9736	0.9734	0.8864	0.9107	1.0000
Seven previous years							0.9827	0.9733	0.9743	0.9225	0.9062
Eight previous years								0.9804	0.9737	0.9510	0.9169
Nine previous years									0.9794	0.9487	0.9502
Ten previous years										0.9829	0.9473
Eleven previous years											0.9802

Table A.4.: Regional tests for HCV with data from previous years.

A.4. Public annual data Netherlands

Sanquin gives public annual reports, on their website, on the numbers of (positive) donors giving the donations in the Netherlands. These numbers are used in Section 2.3.

Year	HBV FTD	HBV RD	HIV FTD	HIV RD	HCV FTD	HCV RD	FTD	RD
2001	23	7	0	3	5	1	61.000	553.000
2002	27	1	0	8	18	3	51.000	482.063
2003	22	9	1	1	9	0	35.000	471.734
2004	23	6	0	4	12	3	43.365	459.643
2005	26	9	1	2	10	1	30.173	433.965
2006	21	5	1	4	5	5	30.173	407.103
2007	15	4	3	3	3	1	27.201	375.621
2008	16	4	2	1	4	0	28.571	366.016
2009	21	13	0	2	10	0	36.146	312.466
2010	18	2	0	1	6	0	37.297	314.786
2011	13	7	1	0	7	0	35.166	305.019
2012	13	6	0	2	4	0	37.468	295.891

Table A.5.: Annual reports on (positive) donors from the Dutch blood bank.

A.5. Calculation on cutting off simulation

Suppose we simulate run lengths X_i but stop the simulations at time t. We denote by $\widetilde{X_t}$ the estimated lengths with the maximum set at t, so:

$$\widetilde{X_t} = \frac{\sum_{i=1}^{n} X_i \cdot 1_{\{X_t<t\}} + t \cdot 1_{\{X_t>t\}}}{n} = \frac{\sum_{i=1}^{n} \min(X_i, t)}{n} \tag{A.1}$$

Recall that a convenient expression for the expected value of a random variable X with non-negative integer values is given by:

$$\mathbb{E}[X] = \sum_{k=0}^{\infty} \mathbb{P}[X > k] \tag{A.2}$$

In case of cutting off the simulation at time t, we have the following probabilities:

$$\mathbb{P}[\min(X, t) > t] = 0 \text{ and } \mathbb{P}[\min(X, t) > k] = \mathbb{P}[X > k] \text{ for } k \leq t - 1 \tag{A.3}$$

Hence when we determine the new expected run length:

$$\mathbb{E}[\widetilde{X_t}] = \sum_{k=0}^{\infty} \mathbb{P}[\widetilde{X_t} > k] = \sum_{k=0}^{t-1} \mathbb{P}[X > k] \tag{A.4}$$

Our error, when we assume our run lengths are geometrically distributed, is the expected difference between X and $\widetilde{X_t}$, becomes:

$$\mathbb{E}[X - \widetilde{X_t}] = \sum_{k=t}^{\infty} \mathbb{P}[X > k] = \sum_{k=t}^{\infty} (1-p)^k = \sum_{k=0}^{\infty} (1-p)^{k+t} = \frac{(1-p)^t}{p} \tag{A.5}$$

We assume we have enough simulations, large n. We assume that the percentage of making an error is, sayϵ on the Average Run Length of the geometrically distributed X, which is $\frac{1}{p}$ (3.25). Then we have:

$$\frac{(1-p)^t}{p} = \frac{\epsilon}{p} \tag{A.6}$$

We obtain an expression for t as we want that $(1-p)^t < \epsilon$:

$$t > \frac{\log(\epsilon)}{\log(1-p)} \tag{A.7}$$

A.6. Simulation results period 4000 weeks

In this section we give the results of the simulation with a pre-determined period of 4000 weeks and 60 infections, see Chapter 6.

	Small shift	Small trend 10 years	Small trend 20 years
Model 1	15.65 (14.79)	19.67 (16.45)	21.62 (15.76)
$CCC-1$	25.12 (25.34)	28.38 (25.56)	28.13 (23.86)
$CCC-2$	23.11 (21.04)	24.70 (21.63)	28.70 (23.52)
$CCC-3$	19.26 (17.75)	23.05 (20.02)	26.92 (21.36)
$CCC-4$	17.38 (14.32)	22.45 (19.37)	24.69 (17.47)
$CCC-5$	16.70 (14.18)	20.47 (16.24)	23.32 (16.28)

Table A.6.: ARL (SRL) detecting small patterns after 4000 stable weeks.

	Moderate shift	Moderate trend 10 years	Moderate trend 20 years
Model 1	7.78 (6.68)	11.49 (7.65)	14.99 (9.13)
$CCC-1$	14.82 (14.35)	18.32 (16.14)	21.71 (17.70)
$CCC-2$	10.88 (10.35)	15.23 (12.20)	19.35 (12.87)
$CCC-3$	9.85 (8.53)	12.77 (8.33)	17.24 (10.28)
$CCC-4$	8.72 (6.98)	12.48 (7.81)	15.88 (8.64)
$CCC-5$	7.72 (6.10)	12.01 (6.80)	15.46 (8.11)

Table A.7.: ARL (SRL) detecting moderate patterns after 4000 stable weeks.

	Large shift	Large trend 10 years	Large trend 20 years
Model 1	2.06 (1.39)	6.90 (3.24)	10.45 (4.57)
$CCC-1$	4.47 (5.04)	10.63 (7.54)	14.81 (9.12)
$CCC-2$	2.47 (2.12)	8.34 (4.26)	11.68 (6.45)
$CCC-3$	2.28 (1.46)	7.64 (3.68)	11.45 (5.00)
$CCC-4$	2.02 (1.48)	7.41 (3.06)	11.13 (4.84)
$CCC-5$	1.83 (1.27)	7.54 (3.05)	10.97 (4.44)

Table A.8.: ARL (SRL) detecting large patterns after 4000 stable weeks.

	First model	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	7.3%	26.9%	21.3%	13.9%	16.3%	14.4%
Moderate shift	5.4%	24.3%	23.7%	14.0%	17.6%	14.9%
Large shift	1.4%	21.5%	23.6%	5.4%	26.9%	21.1%
Small trend 10 years	5.8%	25.6%	24.0%	15.4%	16.9%	12.4%
Small trend 20 years	8.5%	31.3%	19.0%	15.5%	13.3%	12.5%
Moderate trend 10 years	4.3%	24.5%	22.4%	19.4%	14.3%	15.1%
Moderate trend 20 years	6.0%	26.4%	18.7%	19.2%	15.4%	14.3%
Large trend 10 years	8.6%	23.6%	22.2%	16.1%	14.9%	14.6%
Large trend 20 years	7.2%	23.6%	25.2%	15.7%	15.9%	12.4%

Table A.9.: First alarm given in percentage of 500 simulation runs.

	$CCC-1$	$CCC-2$	$CCC-3$	$CCC-4$	$CCC-5$
Small shift	2.6%	0.8%	0.8%	-	-
Moderate shift	-	-	-	-	-
Large shift	-	-	-	-	-
Small trend 10 years	2.0%	1.2%	1.0%	1.2%	0.4%
Small trend 20 years	1.8%	2.0%	1.6%	0.2%	0.6%
Moderate trend 10 years	0.2%	0.2%	-	-	-
Moderate trend 20 years	1.0%	-	-	-	-
Large trend 10 years	-	-	-	-	-
Large trend 20 years	-	-	-	-	-

Table A.10.: Percentage of simulation runs with no alarm given.

	First model	$CCC-r$ charts	Both models
Small shift	7.6%	51.4%	41.0%
Moderate shift	6.0%	45.0%	49.0%
Large shift	1.0%	12.2%	86.8%
Small trend 10 years	7.5%	60.7%	31.8%
Small trend 20 years	9.6%	58.0%	32.4%
Moderate trend 10 years	5.4%	49.2%	45.4%
Moderate trend 20 years	6.4%	56.2%	37.4%
Large trend 10 years	9.4%	40.0%	50.6%
Large trend 20 years	7.8%	50.8%	41.4%

Table A.11.: Percentage of the simulation runs that an earliest year alarm is given by the model.

Bibliography

J. Antoch and D. Jarušková. On-line statistical process control. In C. Lauro, J. Antoch, V. Esposito Vinzi, and G. Saporta, editors, *Multivariate Total Quality Control*, pages 87–124. Physica-Verlag, Heidelberg, 2002.

D. Brook and D.A. Evans. An approach to the probability distribution of CUSUM run length. *Biometrika*, 59:539–550, 1972.

T.W. Calvin. Quality control techniques for "zero defects". *IEEE Trans. Comp. Hybr. Man. Techn.*, 6(3):323–328, 1983.

S. Chakraborti. Run Length Distribution and Percentiles: The Shewhart Chart with Unknown Parameters. *Quality Engineering*, 19(2):119–127, 2007.

L.Y. Chan, D.K.J. Lin, M. Xie, and T.N. Goh. Cumulative probability control charts for geometric and exponential process characteristics. *Int. J. Prod. Res.*, 150(2):420–436, 2003.

A Di Bucchianico and E.R. Van den Heuvel. Shewhart's idea of predictability and modern statistics. In S. Knoth, W. Schmid, and P.-Th. Wilrich, editors, *Frontiers in Statistical Quality Control 11*. Physica-Verlag, 2015.

A. Di Bucchianico, M. Hušková, P. Klášterecký, and W.R. Van Zwet. Performance of control charts for specific alternative hypotheses. In J. Antoch, editor, *COMPSTAT 2004 Symposium*, pages 903–910. Physica Verlag, 2004.

R.J.M.M. Does and B.F. Schriever. Variables control chart limits and tests for special causes. *Stat. Neerlandica*, 46:229–245, 1992.

EMA. *Guideline on epidemiological data on blood transmissible infections*. European Medicines Agency and Committee for Medicinal Products for Human Use (CHMP), 2010.

M. Frisén. Statistical surveillance. Optimality and methods. *International Statistical Review*, 71 (2):403–434, 2003.

M. Frisén. Optimal sequential surveillance for finance, public health, and other areas. *Sequential Analysis*, 28(3):310–337, 2009.

M. Frisén. Methods and evaluations for surveillance in industry, business, finance, and public health. *Qual. Reliab. Engng. Int.*, 27:611–621, 2011.

M. Frisén and J. De Maré. Optimal surveillance. *Biometrika*, 78:271–280, 1991.

H. Gitlow, A. Oppenheim, and R. Oppenheim. *Quality Management: Tools and Methods for Improvement*. Irwin, second edition, 1989.

T.N. Goh. A control chart for very high yield processes. *Qual. Assurance*, 13:18–22, 1987.

M.S. Gold. The geometric approximation to the Cusum run length. *Biometrika*, 76:725–733, 1989.

D.M. Hawkins and D.H. Olwell. *Cumulative Sum Charts and Charting for Quality Improvement*. Springer, New York, 1998.

D.M. Hawkins, P. Qiu, and C.W. Kang. The changepoint model for statistical process control. *J. Qual. Technol.*, 35(4):355–366, 2003.

M.P. Janssen, E.A. Cator, C.L. Van Der Poel, W.P. Schaasberg, G.J. Bonsel, and B.A. Van Hout. Monitoring viral incidence rates: tools for the implementation of European Union regulations. *Vox Sanguinis*, 96:298–308, 2009.

M.P. Kaleta, M.P. Janssen, and E. Cator. Monitoring of viral infection incidence rates in the Netherlands. Technical report, University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Department for Medical Technology Assessment, 2007.

R. Kenett and M. Pollak. On assessing the performance of sequential procedures for detecting a change. *Qual. Reliab. Eng. Int.*, 28(5):500–507, 2012.

T.L. Lai. Sequential changepoint detection in quality control and dynamical systems. *J. Roy. Statist. Soc. Ser. B*, 57:613–658, 1995.

T.M. Margavio, M.D. Conerly, W.H. Woodall, and L.G. Drake. Alarm rates for quality control charts. *Statistics & Probability Letters*, 24(3):219–224, 1995.

D.C. Montgomery. *Introduction to Statistical Quality Control*. Wiley, 5th edition, 2005.

E.S. Page. Continuous inspection schemes. *Biometrika*, 41:100–115, 1954.

G.J.S. Ross and D.A. Preece. The negative binomial distribution. *The Statistician*, 34:323–335, 1985.

Sanquin. Van bloed tot geneesmiddel, 2002.

W. A. Shewhart. *Economic Control of Quality of Manufactured Product*. Macmillan, London, 1931.

W.A. Shewhart. *Statistical Method : From the Viewpoint of Quality Control*. Graduate School of the Department of Agriculture, Washington D.C., 1939.

A.N. Shiryaev. Quickest detection problems: fifty years later. *Sequential Analysis*, 29(4):345–385, 2010.

Z.K. Šidàk. Rectangular confidence regions for the means of multivariate normal distributions. *Journal of the American Statistical Association*, 62 (318):626–633, 1967.

M. Xie and T.N. Goh. Some procedures for decision making in controlling high yield processes. *Qual. Reliab. Engng. Int.*, 8:355–360, 1992.

M. Xie, T.N. Goh, and X.S. Lu. A comparative study of *CCC* and CUSUM charts. *Qual. Reliab. Engng. Int.*, 14(5):339–345, 1998.

M. Xie, T.N. Goh, and V. Kuralmani. *Statistical Models and Control Charts for High Quality Processes*. Kluwer, Boston, 2002.

Nomenclature

ARL	Average Run Length
ARR	Alarm Rate Ratio
BCC	Blood/plasma Collection Center
CCC	Cumulative Counts of Conforming
CL	Center Line
CUSUM	Cumulative Summation
EMA	European Medicines Agency
EWMA	Exponential Weighted Moving Average
FPR	False Positive Rate
GLR	Generalized Likelihood Ratio
i.i.d.	independent identically distributed
Incidence	Number of new cases of an infection expected within a specific time frame
Incidence rate	Number of infections of a disease within a certain population
IRR	Incidence Rate Ratio
MLE	Maximum Likelihood Estimator
Prevalence	Number of cases of an infection at a specific moment within the population
ROC curve	Receiver Operating Characteristic curve
RR	Risk Ratio, relative risk increase caused by one BCC
Sensitivity	see TPR
Specificity	see FPR
SRL	Standard deviation of the Run Length
TPR	True Positive Rate