Wrocław University of Technology
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MASTER THESIS

Simple models of epidemiology

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key words:

epidemiology, mathematical modeling,
agent based models, social networks, MCMC,
computer simulations

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Table of context

Prolog

Thema of this work is epidemiological modeling. This area is explored by researchers from different academic background: physicians, physicists, mathematicians, statisticians, computer scientists and sociologists. All of them have something to add and this work based on different base in different parts from mathematical beginning though computer science (simulations) and concept from physics to finish with sophisticated sociological and statistical analyses. Aim of our work was first to collect few perspective (mostly mathematical) and developed them, but in effect this analyze is more empirical, what make it more practical in use. Models were calibrated on Swedish data, because that country has a huge dataset of citizens and give opportunity to analyze them. This work is also very specious, because of its interdisciplinary and showing light on methods which were not use in epidemiology till this moment. Nobody run simulation representing all citizens of all country to analyze spread of disease (H1N1-influenza pandemic describe in chapter 3) or run MCMC (Markov Chain Monte Carlo) to model disease-MRSA spreading (chapter 5). But before research chapters we consider existing methods. Epidemiological models that treat transmission as "human-to-human" from differential equation point of view do exist in older literature, but in more recent agent-based models appear more often[1]. We have started from general idea of models in this area (chapter 1) with fascinating role of our city- Wrocław, then turn to differential equation models (chapters 1,2). Second part of our thesis is agent-based models (chapters 3,5 and also 4 in some aspects). Mathematical models and computer simulation start to play more significant role as quantity of social interactions is enormous and this is a reason, that this thesis has more simulation than pure modeling. More important than simulations are real data especially register-based. Simulation has sense only if there are some data you can calibrate parameters to run yours simulations. This need enables cooperation between registering institutions which exerts a pressure on collecting data for simple analyse with many researchers who work on new models and use complex tools taken often from other disciplines.

We are presenting our two main research projects:

1 Authors of his publication show how scientific perspective was changing in epidemiology (in case of cholera), Mercedes Pascual, et al.; Hyperinfectivity in Cholera: A New Mechanism for an Old Epidemiological Model? 2006

Calculation for H1N1 cost in Sweden (chapter 3) which is based on MicroSim model of all population of Sweden;

The disease transmission model shows that the incorporation of social structure allows for a more realistic representation of disease spread than do models that assume homogenous mixing. Using this model, it is possible to conduct experiments of significant policy relevance (vaccinating), such as investigating the initial growth of an epidemic on a real-world network. That demonstrate the usefulness of a spatially explicit micro-level representation for policy simulation models in the area of disaster management and in our case Swedish government could look at results of simulation for different scenarios and decide about their intervention to stop epidemic. This model can be observed in real time (prediction was made in September 2009 for winter season 2009/2010) what make it more exiting and also practice.

MRSA spreading in Stockholm hospitals (chapter 5) which is statistical analyse of dataset and quasi-MCMC model to simulate similar situation.

The bacterium meticillin resistant Staphylococcus aureus (MRSA)is known to be the largest care related the infection problem. We investigated the Common Care Registry containing information about all patient visits within Stockholm County during the outbreak period with registry over diagnosed MRSA cases. Methods to analyze the contact network of persons visiting the same care unit is developed within the project as well as methods to analyze in what way network structure affects the transmission of MRSA. We study matrixes of disease transition in hospitals population (infected versus people, who could sent infection). In stationary case: (a)We have matrixes of estimators of that probabilities and other statistical properties of contact networks. In time evolution case: (b)We divided outbreak in smaller, periodical intervals and looked at how MRSA was spreading in time. Quasi-MCMC (Markov chain Monte Carlo) method and artificial networks (main parameter is number of contacts during specific time interval)help us to understand real- and simulated-paths of disease transition. Matrixes of probabilities (b) were used to find mechanism of change states (vectors of all population 0-health or 1-ill)and we can run quasi-MCMC to get most likely paths.

We have added also few word about cellular automata and how we can use them in epidemiology (chapter 4).

Acknowledge

We would like to thank Ph.D. Lisa Brouwers (Swedish Institute for Infectious Disease Control) for inviting me to DSV department in Stockholm and giving me chance to analyse H1N1 model (chapter 3); Ph.D. Frederik Lilieros and M.Sc. Lu Xin (Department of Sociology, University of Stockholm) for releasing unique dataset of MRSA patient and for giving sociological advises in coupling with that data (chapter 4); Dr Barlomiej Dybiec (Institute of Physics, Jagiellonian University) for explaining his CA-simulations (chapter 5); and my supervisor prof. Wojciech Okrasiński (Institute of Mathematics and Computer Science, Technical University of Wroclaw) for helping with literature (especially chapters 1 and 2).

To run calculation or simulation we have used some mathematical and statistical tools: *Statistica* (chapter 5), *MS Excel* and *OpenOffice Calc* (chapter 3), *Matlab* (chapter 2,3), *Pajek* (chapter 5). I have written also programs and applications in *Visual Basic* (chapter 5) and *C++* (chapter 4).

1)Epidemics

1.1)Introduce

An *epidemic* (from Greek epi- upon + demos people) an occurrence of disease that is temporarily of high prevalence. The rise and decline in epidemic prevalence of an infectious disease is a probability phenomenon dependent upon transfer of an effective dose of the infectious agent from an infected individual to a susceptible one[2]. The same phenomena is called *epizootic* by animals and *epizitofic* by plants. In recent usages, the disease is not required to be communicable; examples include cancer or heart disease, but we concentrate only those with transmission in this work. If epidemic occurring over a wide geographical area (e.g., worldwide) is called a *pandemic.* Nowadays we have a lot of examples of pandemics and this problem will be solving. Who didn't hear about swine flu during spring 2009 or bird flu in 2005?

Science, which cope with epidemics is epidemiology. Epidemiological studies may be classified as descriptive or analytic. In descriptive epidemiology, demographic surveys are used to determine the nature of the population affected by the disorder in question, noting factors such as age, sex, ethnic group, and occupation among those afflicted. Other descriptive studies may follow the occurrence of a disease over several years to determine changes or variations in incidence or mortality; geographic variations may also be noted. Descriptive studies also help to identify new disease syndromes or suggest previously unrecognized associations between risk factors and disease. In addition to providing clues to the causes of various diseases, epidemiological studies are used to plan new health services, determining the incidence of various illnesses in the population to be served, and to evaluate the overall health status of a given population. In most countries of the world, public-health authorities regularly gather epidemiological data on specific diseases and mortality rates in their populaces.[3] Main field of their studies focus on non-interacting systems. Most of knowledge came from analytical analysis and tests. These studies divide a sample population into two or more groups, selected on the basis of suspected causal factor (for example, cigarette smoking) and then monitor differences in

2 Encyclopaedia Britannica *„Epidemic"*
3 Encyclopaedia Britannica *„Epidemiology"*

incidence, mortality, or other variables. This way of studying statistical properties can be supplemented by modeling. Especially if sending an infection is a point in disease. In results governments undertaking multidisciplinary programmes of state health policy such as Programme of Prophylactic Vaccination. Data for the year 1999 provided by State Institution of Hygiene display that it is most important that the downward trend in morbidity from infectious diseases kept up throughout the whole last decades (from 3,1 in 1970 to 0,7 in 1999 death on 10000 in population). However pediatricians and epidemiologists are most worried by rising numbers of TB cases diagnosed in children of 0-14 years of age observed over last three years. Data provided by the Chief Sanitary Inspector display that incidence of tuberculosis in 2001 was 20% up on the previous year's among children aged 0-14 which was accompanied by increase in sputum-positive children.[4] That means, what some of disease, which were called „death" appear in developed countries with some probability. A programme of „prophylactic care in environment", based on theoretical assumptions with stress put on health promotion was launched as an answer.

Mathematical models can help in describing phenomena of epidemiology spreading and give an answer how to fight with them. There are many problems in modeling because of big variety of epidemic types. Many of epidemics appeared in developed countries, such as colds or influenza, cause only temporal disease to most sufferers, although economically (in terms of medical cost or employment) their effects may be substantial. On the other hand in undeveloped countries experienced diseases such cholera, and cause large numbers of death, especially if treatment is not available.

We have to consider different types of transmission from an infected host to aninfexted susceptible. Transmission may be by contact as for example, in the case of measles; alternatively it may involve an intermediate host, such as mosquito in case of malaria. Another possibility is virus causing disease in free in environment, as in case with air or water borne virus. In contact case are more subgroups(like in venereal diseases). Also, some disease, such as measles, usually confer life long immunity.

Typical questions which the public health authorities are likely to need answers to are:

4 Janusz Szymborski (2003) „Ochrona zdrowia dzieci i młodzieży w Polsce-aktualne problemy i propozycje rozwiązań systemowych"

●If an infection introduced into society at what rate will it spread?
●How many initial infections are required to cause an eventual epidemic?
●When will and epidemic be its worst?
●Does the number of individuals are contact the disease settle down to some fixed value (i.e. a 'steady state or equilibrium value')? If so, is this a stable situation?
●How quickly must invectives be removed from society by say isolation, if one is to prevent an epidemic developing?
●Does the number if invectives follow any specific pattern?

1.2)Historical Aside on Epidemics

There is a lot of written information about great epidemics in history of men. Plague appears in Bible and seems to be first description of this disease. „For a death-dealing confusion had occurred in the whole city; the hand of the [true] God had been very heavy there, and the men that did not die had been struck with piles" 1 Samuel 5:11,12.

Greek historicist Thucydides described in great details Plague of Athens (430 BC). He wrote:
"As a rule, however, there was no ostensible cause; but people in good health were all of a sudden attacked by violent heats in the head, and redness and inflammation in the eyes, the inward parts, such as the throat or tongue, becoming bloody and emitting an unnatural and fetid breath."
"These symptoms were followed by sneezing and hoarseness, after which the pain soon reached the chest, and produced a hard cough. When it fixed in the stomach, it upset it; and discharges of bile of every kind named by physicians ensued, accompanied by very great distress."
"In most cases also an ineffectual retching followed, producing violent spasms, which in some cases ceased soon after, in others much later." (Translation by M.I. Finley in „The Viking Portable Greek Historians")

Thucydides didn't mention nothing about a person to person contact with applying to this disease. I was firstly raised in the 19th century. The most important for Europe history „Black Death" in middle 14th century wasn't also explained by a network of contacts. More realistic were causes like evil exhalation from earth or aerial masmata. Plague from middle ages took 1/3 victims from whole population.

During ages appear phenomena, which is called by demographers epidemiological transition. The main process is a transition from communicable or infectious diseases to man-made disease as a cause of mortality. In deed, knowledge of causes of death in less developed population based on bacteria and virus. Data provided by UN in typical population with big proportion of young people and quit big mortality about 35% of death are caused by infectious and respiratory diseases, 25% cardiovascular diseases and cancer. Instead that in typical population with big proportion of old people and quit low mortality with first group of death is connected less than 5% of deaths, with second more than 80%. According to this concept dynamic of population change in not cause by natality, but by morbidity. The same oscillation are observed in animal world. Mathematical model of Volterra-Lotka shows how 2 populations of predator and pray are changing in time. That extraordinary deaths are sometimes called catastrophic and in human world ware caused by epidemics, famine etc. A. R. Orman suggested sequence of 3 types of mortality[5]: age of plagues(big fluctuations in cycles of famine and epidemics); age of expiring epidemics(much more systematic deaths and much less fluctuations); age of man-made disease (stable level of deaths). We can think, then in last phase epidemics should not appear. Unfortunately old people in modern societies are more vulnerable to infectious diseases. They often live in crowded cities and infectious diseases can get in to synergy with old-people -diseases. Parallel appeared new species resistant to drugs. They caused growth in some almost forgotten diseases. For example Ebola virus was discovered in 70th; Human immunodeficiency virus (HIV) and Hepatitis C in 80th; hemorrhagic fever in 90th. Their role in mortality is quit big, with notation that AIDS is 4th mainly cause of death on earth.

5 A. R. Orman *„Epidemiologic transition. A theory of epidemiology of population change"* Milbank Memorial Fund Quarterly 1971, vol. 49

1.3)Bernoulli's model

I simply wish that, in a matter which so closely concerns the well-being of mankind, no decision shall be made without all the knowledge which a little analysis and calculation can provide.

Daniel Bernoulli, presenting his estimates of smallpox

Royal Academy of Sciences-Paris, 30 April 1760

1.3a)Introduction

This Swiss mathematician was the first to express the proportion of susceptible individuals of an endemic infection in terms of the force of infection and life expectancy. His work describe smallpox, which cause a lot of epidemics in big European cities at his time. Smallpox devastated earlier the native Amerindian population and was an important factor in the conquest of the Aztecs and the Incas by the Spaniards. In Poland smallpox last time appear in Wroclaw in 1963, but it was stopped by the actions of the government and epidemiologists moreover smallpox was eradicated by WHO in 1979. Bernoulli actually used date provided from Wroclaw to estimate his model. He based at work of famous British astronomer – Edmund Halley „An Estimate of the Degrees of the Mortality of Mankind, drawn from curious Tables of the Births and Funerals at the City of Breslaw" published in Philosophical Transactions 196 (1692/1693). In 17^{th} century English Breslaw means Breslau-German name of Wroclaw. In beginning of his publication Halley wrote his purpose: „This *Defect* seems in a great measure to be satisfied by the late curious Tables of the Bills of *Mortality* at the City of *Breslaw,* lately communicated to this Honorable Society by Mr. *Just ell*, wherein both the *Ages* and *Sexes* of all that die are monthly delivered, and compared with the number of the *Births*, for Five Years last past 1687, 88, 89, 90, 91, seeming to be done with all the Exactness and Sincerity possible." Later he described Wroclaw: „This City of *Breslaw* is the Capital City of the Province of *Silesia*; or, as the *Germans* call it, *Schlesia*, and is situated on the Western Bank of the River *Oder*, anciently called *Viadrus*; near the Confines of *Germany* and *Poland (...)* It is very far from the Sea, and as much a *Mediterranean* Place as can be

desired, whence the confluence of Strangers is but small, and the Manufacture of Linnen employs chiefly the poor People of the place, as well as of the Country round about; whence comes that sort of Linnen we usually call your Schlesie *Linnen*; which is the chief, if not the only Merchandize of the place. For these Reasons the People of this City seem most proper for a *Standard*; and the rather, for that the *Births* do, a smaller matter, exceed the *Funerals*. The only thing wanting is the Number of the whole People, which in some measure I have endeavored to supply by comparison of the *Mortality* of the People of all Ages, which I shall from the said Bill traces out with all the Accuracy possible."

Bernoulli's main objective was to calculate the adjusted life table if smallpox were to be eliminated as a cause of death. His formula is valid for arbitrary age-dependent host mortality, in contrast to some current formulas which underestimate herd immunity.

Bernoulli wrote:
(1) I shall assume that, independent of age, in a large number of persons who have not had smallpox, the disease annually attacks one person out of as many persons as there are units in the number n. According to this hypothesis, the danger of catching the disease would remain the same at every age of one's life, provided that one had not already had it. If, for example, we put n=10, it would be the fate of every person to be decimated every year of his life in order to know whether he would have smallpox this year or not, right up to the moment when that fate actually befell him. This hypothesis seems to me to be very probable for all young people up to the age of sixteen to twenty years. If we see few people over that age who catch smallpox, it is because the great majority have already been infected by it. What follows will enable us to see what degree of probability this hypothesis merits.
(2) In the second place, I shall assume that, at whatever age one catches smallpox, the danger of dying of it is always the same and that out of a number of patients expressed by the number m, one dies of it. With regard to this assumption, I note that no doctor would take it into his head to suppose that, other things being equal, smallpox is more or less dangerous merely on account of the age at which it is caught, provided that this age does not exceed twenty. It is only above this age that we usually suppose that smallpox becomes a little more dangerous. We shall later have occasion to examine this hypothesis more closely.

In practice he starts from M. Halley's Table with 1000 who reach the age of one complete year and later with number of survivors. Bernoulli supposed that there were born 1300 children, from which 1000 survived to first year.

Age. Curt.	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**
1	1000	8	680	15	628	22	585	29	539	36	481
2	855	9	670	16	622	23	579	30	531	37	472
3	798	10	661	17	616	24	573	31	523	38	463
4	760	11	653	18	610	25	567	32	515	39	454
5	732	12	646	19	604	26	560	33	507	40	445
6	710	13	640	20	598	27	553	34	499	41	436
7	692	14	634	21	592	28	546	35	490	42	427
Age. Curt.	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**	**Age. Curt.**	**Per sons.**
43	419	50	346	57	272	64	202	71	131	78	58
44	409	51	335	58	262	65	192	72	120	79	49
45	397	52	324	59	252	66	182	73	109	80	41
46	387	53	313	60	242	67	172	74	98	81	34
47	377	54	302	61	232	68	162	75	88	82	28
48	367	55	292	62	222	69	152	76	78	83	23
49	357	56	282	63	212	70	142	77	68	84	20

Table 1.1. Survived table of Wrocław [M. Halley's]

1.3b)Mathematical description

He set some variable to describe his model:

–the present age, expressed in years=x;

– the number of survivors at this age=ζ;

– the number of those who have not had smallpox at this age=s;

– and let us retain the meaning given above to the letters m and n .

Here is the reasoning which can be followed to find a general expression for.

$$-ds = \frac{sdx}{n} - \frac{sd\zeta}{\zeta} - \frac{ssdx}{mn\zeta}$$ **(Eq 1.1)**

Change of s is negative, because s is decreasing in time. On the Right hand side we have: number of people who catch smallpox in time interval; number of people who died; appendix describe how many people died of smallpox.

We can derive that equation doing substitution:

If we put $\frac{\zeta}{s} = q$ **(Eq 1.2)**, we have $\frac{dq}{dx} = \frac{q}{n} - \frac{s}{mn}$ **(Eq 1.3)**

and hence finally $s = \frac{m}{e^{\frac{x+C}{n}} + 1}\zeta$ **(Eq 1.4)**

Putting initial condition at x=0, s=ζ (each letter then expressing the number of newborn children involved)

$$s = \frac{m}{(m-1)e^{\frac{x}{n}} + 1}\zeta$$ **(Eq 1.5)**

Bernoulli put in his consideration m=8 and n=8.

$$s = \frac{8}{7e^{\frac{x}{8}} + 1}\zeta$$ **(Eq 1.6)**

That last equation was used to construct the Table at the end of this Memoir. Here is the explanation of it (in Bernoulli's words):

The column shows the ages by completed years, which I have denoted by , starting with 0 which corresponds to the day of birth.
The column shows the number still alive at each age out of the total of 1300, whom I take as all born on the same day. This column is based on M. Halley's Table. These numbers are denoted by the variable.
The column is based on the final equation of the previous paragraph, so that it gives, for each age, the number who, according to my hypothesis, have not yet had smallpox.
The column, on the other hand, gives the number who have already had smallpox and have recovered from it, and have not died of any other diseases. They are expressed by .
The column shows the number who will probably have caught smallpox during the previous year. This is, according to my hypothesis, one eighth of all those who have not

yet had it, or s/8; but, for greater exactitude, I shall here take for not the value which we have found for the beginning of each year, but for the middle of the preceding year; that is to say, I shall take the arithmetic mean between the two numbers of the third column which follow each other. Thus the first number of this fifth column shows how many new-born children will have caught smallpox during their first year of life.

The column shows the number who die of smallpox during the year which we have described. Thus, according to my hypothesis, all these numbers are one eighth of the corresponding numbers of the fifth column. The column shows the sum of all who have died of smallpox from birth up to each completed year of life.

The column shows the number whom all other diseases, apart from smallpox, carry off during each current year. Thus, each number of this column is the difference between the total deaths of the past year, which we know from the second column, and those who have died of smallpox during the same past year.

Age in years	Survivors according to Halley	Not having had smallpox	Having had smallpox	Catching smallpox each year	smallpox each year	Totall smallox deaths	Death of other diseases each year
0	1300	1300	0				
1	1000	896	104	137	17,1	17,1	283
2	855	685	170	99	12,4	29,5	133
3	798	571	227	78	9,7	39,2	47
4	760	485	275	66	8,3	47,5	30
5	732	416	316	56	7	54,5	21
6	710	359	351	48	6	60,5	16
7	692	311	381	42	5,2	65,7	12,8
8	680	272	408	36	4,5	70,2	7,5
9	670	237	433	32	4	74,2	6
10	661	208	453	28	3,5	77,7	5,5
11	653	182	471	24,4	3	80,7	5
12	646	160	486	21,4	2,7	83,4	4,3
13	640	140	500	18,7	2,3	85,7	3,7
14	634	123	511	16,6	2,1	87,8	3,9
15	628	108	520	14,4	1,8	89,6	4,2
16	622	94	528	12,6	1,6	91,2	4,4
17	616	83	533	11	1,4	92,6	4,6
18	610	72	538	9,7	1,2	93,8	4,8
19	604	63	541	8,4	1	94,8	5
20	598	56	542	7,4	0,9	95,7	5,1
21	592	48,5	543	6,5	0,8	96,5	5,2
22	586	42,5	543	5,6	0,7	97,2	5,3
23	579	37	542	5	0,6	97,8	6,4
24	572	32,4	540	4,4	0,5	98,3	6,5

Table 1.2. *Smallpox in Wroclaw [D. Bernoulli]*

1.3c)Results

Bernoulli has constructed the second Table at the end of this Memoir, in which the first

two columns are the same as in the first Table, though he has given the second column another name, ‘natural state with smallpox’, in contradistinction to the third column, which shows the ‘state without smallpox’ and which gives the number of survivors each year assuming that nobody must die of smallpox. Difference between second and third column gave him a gain in people's lives. He introduced ‘total quantity of life’ of the whole generation, for each of the two states, for the sum of all the numbers of the second column and of the third column respectively (table 1.3). Making this deduction, we obtain the total quantity of life for the state free from smallpox, with the whole tribute paid, which must be compared with tribute for the natural state. If take expected values of variables in second in third column (sum all multiplication of age and values in column and we divide these numbers by 1300) we will have the average life for the natural state as 26 years 7 months, for the state without smallpox and without tribute as 29 years 9 months and for the state free from smallpox. Under these assumptions an individual’s expectation of life at birth would increase from 26 years 7 months to 29 years 9 months.

Age in years	Natural state with smallpox	State without smallpox
0	1300	1300
1	1200	1171
2	855	881,8
3	798	833,3
4	760	802
5	732	779,8
6	710	762,8
7	692	749,1
8	680	740,9
9	670	734,4
10	661	728,4
11	653	722,9
12	646	718,2
13	640	741,1
14	634	709,7
15	628	705
16	622	700,1
17	616	695
18	610	689,6
19	604	684
20	598	678,2
21	592	672,3
22	586	666,3
23	579	659
24	572	651,7
25	565	644,3

Table 1.3. Gain in life [D. Bernoulli]

There are some parameters, which are used today, introduced by Bernoulli: force of infection *1/n* (the annual rate of acquiring an infection) the case fatality *1/m* (the proportion of infections resulting in death). If *L* is life expectancy, then the proportion of susceptible individuals *u* Bernoulli estimated the susceptible proportion using the expression $u=1/m/(L/n)$. From several large cities (not only Wroclaw) which recorded cause-specific numbers of deaths, estimates of *1/m* were known to be about 1/13 so 7.7%. Bernoulli used Halley's life table for the city of Wroclaw and came up with the estimates $1/n = 1/8$ and also $1/m = 1/8$ so 12.5%. For Paris he assumed a life expectancy of 32 years which yields a proportion of susceptible individuals of 15%.

2)Differential equations

2.1)The simplest model

In first instance let consider the spread of a non-fatal disease, to which no-one is naturally immune. Suppose the population can be divided into two groups: Susceptible-Healthy and Infectious-Infected.

Assume that at general time *t*:

S(t) = Number of Susceptible
I(t) = Number of Invectives
with *S(t)+I(t) = N*
The problem now to model spread of the disease.
Consider a single *susceptible* individual in a homogeneously mixing population. This individual contacts other members of the population at the rate *C* (with units time^{-1}) and a proportion *I/N* of these contacts are with individuals who are infectious. If the probability of transmission of infection given contact is β, then the rate at which the infection is transmitted to *susceptibles* is β*CI/N*, and the rate at which the *susceptible* population becomes *infected* is β*CSI/N*.
The *contact rate* is often a function of population density, reflecting the fact that contacts take time and saturation occurs. One can envisage situations where *C* could be approximately proportional to *N* (which corresponds to mass action), and other situations where *C* may be approximately constant. Hence terms like β*SI* and β*SI/N* are frequently seen in the literature. For these, and in many instances where the population density is constant, the contact rate function *C* has been subsumed into β, which is now no longer a probability but a "transmission coefficient" with units time^{-1}. To reduce number of coefficient let write: *r*= β*C/N*. The number of invectives at time *t* is given by the differential equation

$$\frac{dI}{dt} = rSI \quad \textbf{(Eq 2.1)}$$

So after recalculation

$$\frac{dI}{dt} = r(N-I)I \quad \textbf{(Eq 2.2)}$$

This is a very famous result, and is known as logistic equation. To get this equation let separate integrate both sides of Eq 2.2.

$$\int \frac{dI}{I(N-I)} = \int r\,dt$$

$$\int \left(\frac{A}{I} + \frac{B}{(N-I)}\right) dI = \int r\,dt$$

Solution of that integration:

$$\frac{1}{N}\ln\left(\frac{I}{N-I}\right) + C_0 = rt$$

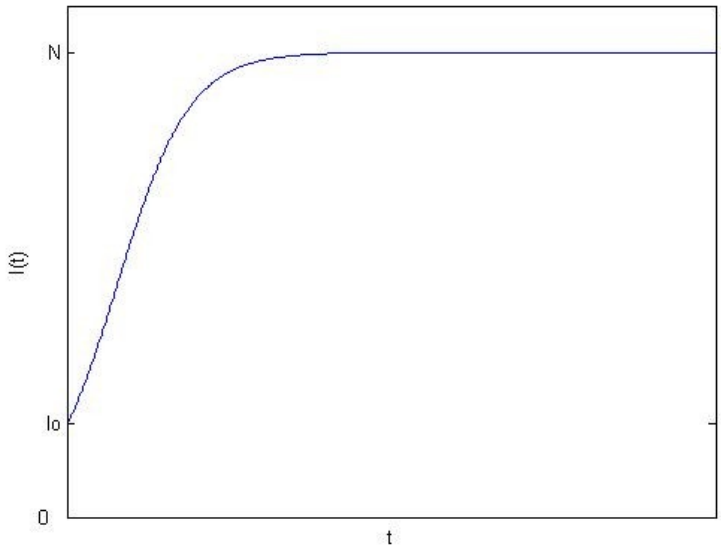
$$\frac{I}{N-I} = C\exp(Nrt)$$

and we can derive *I*:

$$I = \frac{N I_0}{\frac{I_0}{C}\exp(-Nrt) + I_0}$$

Assuming that initially, when t=0, there are I_0 infected individuals, then our differential equation may be rapidly solved $C = \frac{I_0}{N - I_0}$ to give

$$I(t) = \frac{N I_0}{I_0 + (N - I_0)\exp(-rNt)} \quad \textbf{(Eq 2.3)}$$



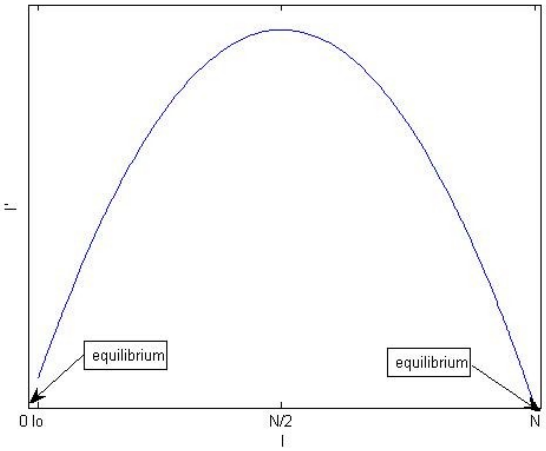
Graph 2.1. Spread of Disease for Simple Model [A. Jarynowski]

It follows that in this case there are two states of equilibrium corresponding respectively to $I(t)=0$ and $I(t)=N$

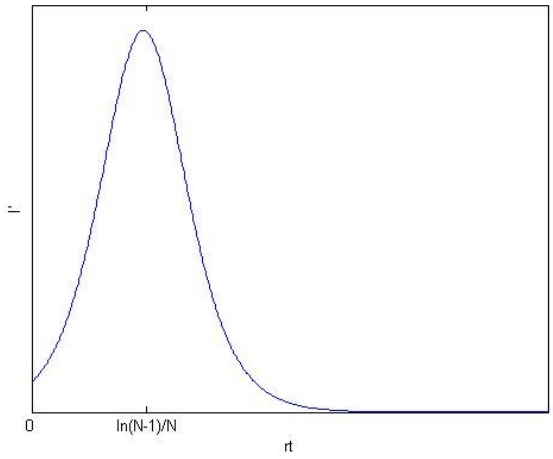
Such a graph referred to a phase plane. The concern is only with values of I in the interval $[0,N]$, indicating that $I'(t)>0$ which means that number of infectives is increasing. By inspection of figure it is seen that the arrow approaches the equilibrium state $I=N$ for all permissible values of I. This means that the number of invectives will tend to the equilibrium state N, no matter how many invectives are initially present. Thus $I(t)=0$ is referred to as an unstable equilibrium state.

In practice one is interested in the rate of speed of the epidemic.

This plot (graph 2.1)is known as the epidemic curve and it can be shown that maximum activity occur when $rt=(ln(n-1))/N$ corresponding to the situation when half the population is infected.



Graph 2.2. Phase plane plot [A. Jarynowski]



Graph 2.3 Epidemic curve [A. Jarynowski]

2.2)Putting in recovery

It was concluded in the previous section that epidemics spread rapidly through a closed community, when it is reasonable to assume that there are no recoveries during the period of epidemic. However it is not valid in most cases. Thus development of model allow possibility of recovery. Following recovery, and individual either becomes immune to the disease or again becomes susceptible to it.

Initially we will couple with second case. Looking at the recovery term we assume that it is proportional relationship with invectives. It gives:

$$\frac{dI}{dt} = rSI - aI \quad \textbf{(Eq 2.4)}$$

so after recalculation

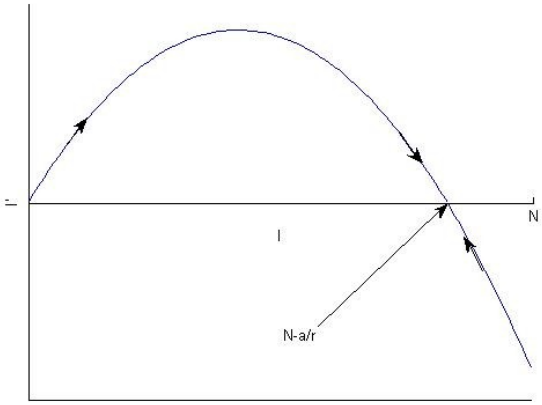
$$\frac{dI}{dt} = I(rN - Ir - a) \quad \textbf{(Eq 2.5)}$$

Equilibrium states occur when *I'*=0, so that

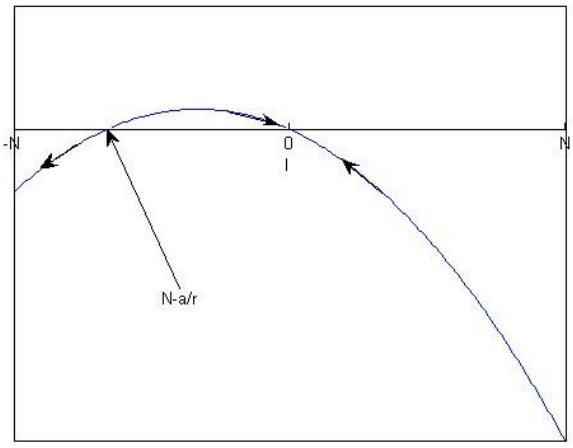
I(t)=0 and *I(t)=N-a/r*

Three different cases arise dependent on the sign of *N-a/r*

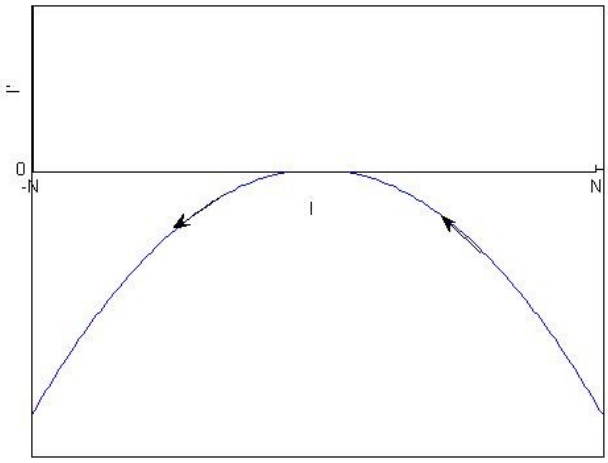
1)*N>a/r*



2)*N<a/r*



3)*N=a/r*



Graph 2.4 Plane plot for model incorporating recovery 1) 2) 3) [A. Jarynowski]

It is clearly seen that $I=N-a/r$ is a stable state whilst $I=0$ is unstable state. Thus is the disease is introduced into society, then if $a/r<N$, it will always remain in the society reaching a stable situation.
$I(t)=N-a/r$ and $S(t)=a/r$ is the epidemic state.

2.3)Allowing of replenishment

Suppose that population is divided into three classes: the susceptibles (S) who can catch the disease; the infectives (I), who can transmit disease and have it; and the removed (R) who had the disease and are recovered (with immune) or isolated from society. Schema of transition can be represented:

$$S \to I \to R$$

The model mechanism may be updated to following form:

$$\frac{dI}{dt} = rSI - aI, \quad (\textbf{Eq 2.6})$$

$$\frac{dS}{dt} = -rSI, \quad (\textbf{Eq 2.7})$$

$$\frac{dR}{dt} = aI, \quad (\textbf{Eq 2.8})$$

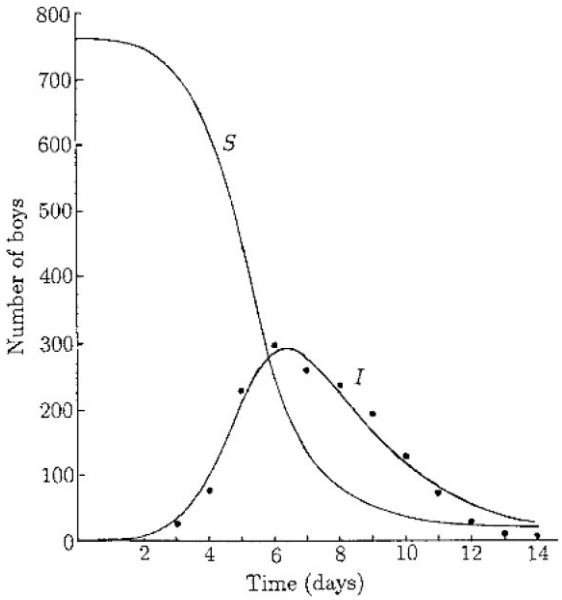
A key question in for given r, a, S_0, I_0, whether the infection will spread or not and if it

how it develops in time and when it start to decline. Since initial condition on *S*- $S_0<a/r$ then $dI/dt<0$ in which case $I_0>I(t)$ and *I* goes to 0 with *t* going to infinity. On the other hand if $S_0>a/r$ then *I(t)* increase and appear epidemic. We have something like threshold phenomenon S_c and depend on level of initial numbers. Inversion of this critical parameter is infection's *contact rate (=r/a).*

We can write:

$$R_0=\frac{r S_0}{a} \quad \textbf{(Eq 2.9)}$$

where R_0 is basic reproduction rate of the infection. This rate is crucial for dealing with and an epidemic which can be under control with vaccination for example. Action is needed if $R_0>1$, because epidemic clearly ensues then.



Graph 2.4 Influenza epidemic data (●) for a boys boarding school as reported in UK in 1978. The continous curves for *I* and *S* were obtained from a best fit numerical solution of SIR system with parameters: S_0=762, I_0=1, S_c=202, *r*=0,0022/day. The condition of epidemic occur, $S_0>S_c(=a/r)$ [graph by J. Murray]

Other assumption for developing model is to incorporate the possibility of replenishment in the number of healthy susceptibles.

$$S \rightarrow I \rightarrow R$$

This may be in form of new births, immigration or by the loss of immunity of some whose have had the disease and recovered. On the basics of a constant replenishment rate u which is new in model (u is only difference between Eq 2.11, Eq 2.12 and Eq 2.7, Eq 2.8).

$$\frac{dI}{dt} = rSI - aI, \quad (\textbf{Eq 2.10})$$

$$\frac{dS}{dt} = -rSI + u, \quad (\textbf{Eq 2.11})$$

$$\frac{dR}{dt} = aI - u, \quad (\textbf{Eq 2.12})$$

It is rapidly seen that $S(t)=a/r$ and $I(t)=u/a$ are an equilibrium state corresponding to Eq. 2.10-12.

Of course this model can be more complicated, but without change in this system of equations. Our parameter u, which describes replenishment from R to S can be understand as a migration rate and taking initial condition of R we have possibility to build reservoir of population, which can migrate into system.

That few simple models are only beginnings of this work and give one base for futher consideration and more sophisticated (but not in terms of differential equation) models

3)Economic Consequences to Society of Pandemic H1N1 Influenza[6]

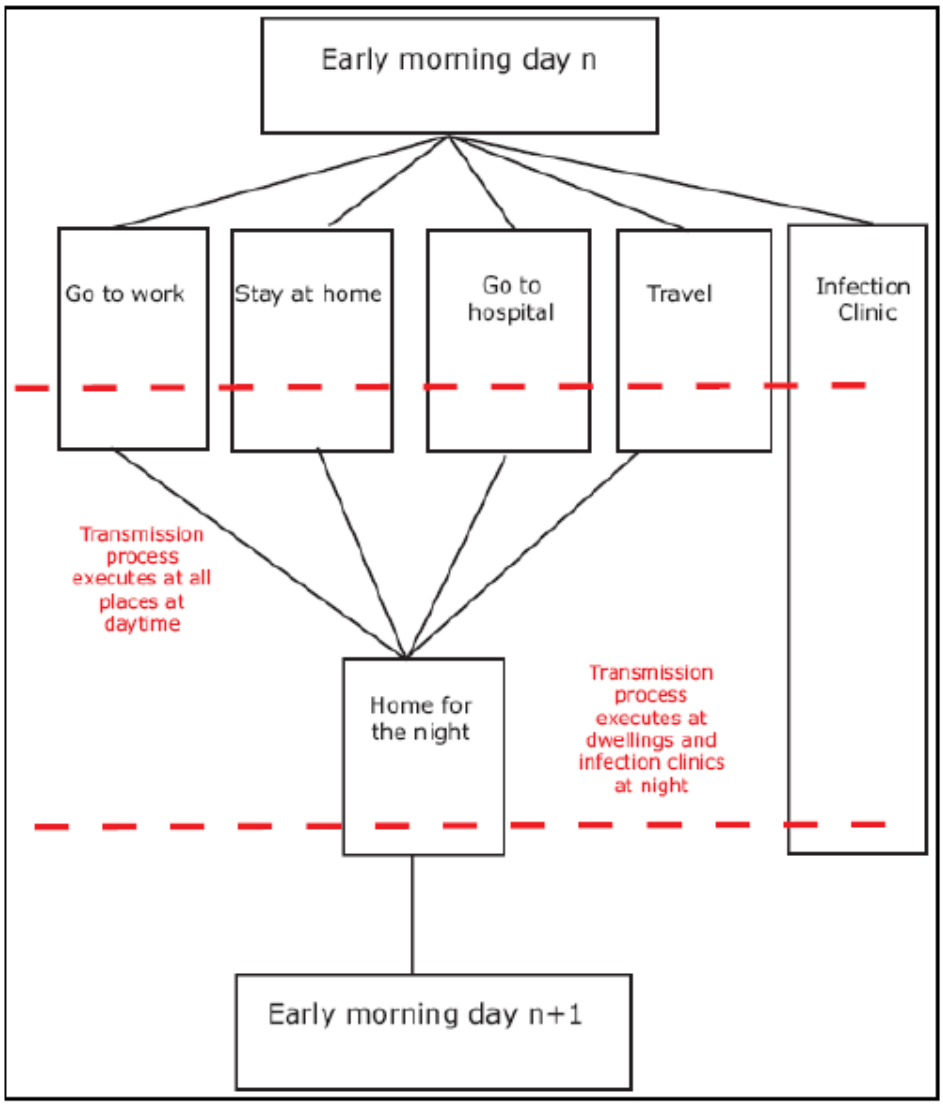
3.1)MicroSim Model

Traditionally SIR-models have been used to aid the understanding of these processes (what we were showing in previous chapters). SIR is a compartmental model in which differential equations govern the dynamic flow between three compartments and no contact structure is assumed. In an SIR-type model, the population is split into three different groups and the majority of the population is placed in the susceptible compartment. All information about society is used in microsimulation, so it can give better prediction, then differential equations. Simplified compartmental models provide inadequate representations because contacts between susceptible and infectious persons are not random[7]. We can use a lot of information in this consideration, which are provided by government. Another reason is that, there is possible to run algorithms for society of whole country-Sweden and there are not too time consuming, e.g. one 180 day simulation take about less than 1h on personal computer.

Database of programme takes account data from:
1. National population register- all information about sex, age etc
2. Employment register- it provides list of employee or students
3. Geography database -100x100 coordinates of houses, schools, hospitals or workplaces

Disease transmission is performed twice daily at 9 am and 5 pm. Programme checks where are all persons during that day hours and night hours. The house member lists and patient lists are iterated to calculate the combined infectiousness of their members. In the case of larger workplaces, the member lists are further divided into departments. After the combined infectiousness is determined, the list members are exposed and infected according to infection risk.

6 I was involved in that project. Results were used in govermantal purpose and published in swedish: „Belastning på samhället vid ett utbrott av den nya pandemiska influensan A(H1N1) 2009" 2009
7 Liljeros, F. et al (2001). "The web of human sexual contacts"



Picture 3.1 The daily routines for the simulated persons. [L. Brouwers][8]

Additional contacts (and transmission) are included in model in two ways (Sweden is divided into 81 regions with their own characteristics of density or intensivity of traveling):

1.Neighbourhood

2. Travel[9]

Infectionous scheme depends on level of illness. Carrat[10] introduced profile which was used by authors of model in sense of Weibull distribution. After some calibration it was

8 L. Brouwers „Microsimulation Models for Disaster Policy Making" Stockholm University Series (1995)

9 Statens Institut för Kommunikationsanalys SIKA. RES 2001. Den nationella reseundersökningen : http://www.sika-institute.se/Doclib/Import/100/ss2002_2.pdf [active on 01.2010]

10 Carrat F, et al.A 'small-worldlike' model for comparing interventions aimed at preventing and controlling influenza pandemics. 2006

found that the best probabilities give transmission coefficient R_0 at level 1,4.

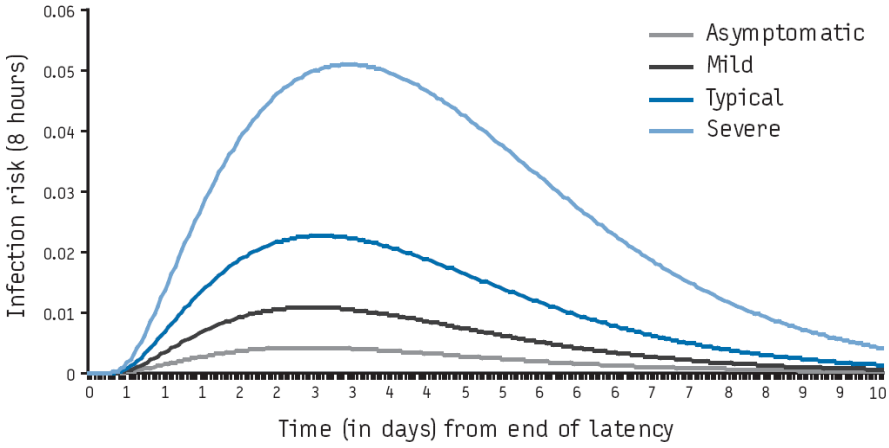


Figure 3.12. Profile of probability of sending infections for adults in MicroSim model[11][12] [adopted F. Carrat]

3.2)Realization in epidemiology

In cooperation with the epidemiological unit at the Swedish National Board of Health and Welfare, researchers at the Swedish Institute for Infectious Disease Control and the Royal Institute of Technology and Department of Computer and Systems Sciences of Stockholm University micro-modeled the effect of a possible future scenario of an outbreak of pandemic flu in Sweden, projected for the autumn and winter of 2009. An executable simulation model was used together with registry data from Statistics Sweden to link the entire Swedish population together in a large spatially explicit social network. The overall aim of developing the model has been to allow for the simulation of the spread of infection in a population in a realistic manner, and examine the effects of applying different policy strategies. In the social network, each person has links to family members, workplace, home, and the nearest health care facility. Individuals in the model go to kindergarten, schools, work, healthcare facilities, and travel to other places where they may be exposed to the risk of infection. Since all places have explicit coordinates,

11 Moser MR, Bender TR, et al.. An outbreak of influenza aboard a commercial airliner. 1979
12 Ferguson NM, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. 2005

the geographical spread can be studied.

To compare the economic consequences to society of different scenarios of spread, costs were included for absenteeism due to illness, absenteeism due to child care, medical visits in primary care, hospitalization, and for vaccination. In particular, to analyze the effects of vaccination as predicted by model experiments.

Results are preliminary and based on assumptions about the infectiousness and morbidity of the pandemic, which both are in the current situation uncertain, as well as several crude assessments of health economic factors. When comparing the different scenarios, however, certain differences may be expected to persist even if the infectivity and the overall disease picture would change. This view will have to be confirmed by further experiments, which are already under way.

The simulations were run with the following assumptions. The outbreak of pandemic influenza in Sweden starts depend of method in June or in September. R0-value corresponding approximately to 1.4 in main model, because that was observed in New Zealand during their outbreak. The viral infectivity is markedly initially R_0 value of approximately 2.1 in preliminary method

$$R_0 = \frac{-\ln(\frac{A}{S_0})}{1-\frac{A}{S_0}} \quad \textbf{(Eq 3.1)}$$

Immunity was calibrated in model to obtain R_0- 1.4[13]

S_0: Total number of susceptible individuals before the outbreak

A: Total number of susceptible individuals after the outbreak

Children and adolescents are assumed more susceptible, and more infectious, then adults. For all ages, the following allocation of morbidity holds: 16% are asymptotically ill (i.e.,

13 This formula is defined as is the average number of individuals a typical person infects under his/her full infectious period, in a fully susceptible population. We have to take it as a aproximation only and it can not be consider the same as eq 2.9, but both values have the same meaning. It was proposed by Brouwers L, Cakici B, Camitz M, Tegnell A, Boman M. Economic consequences to society of pandemic H1N1 influenza 2009 – preliminary results for Sweden

show no symptoms), 34% are mildly ill, 40% display a typical illness, while 10% have a severe form of illness. One adult in the household stays home from work if a child younger than 12 years is sick, and the same holds in the case of school closure.

To compare the societal costs of the scenarios, the following costs—obtained from health economists at the Swedish Institute for Infectious Disease Control—were used.

- Cost of one day's absence from work, for a worker: SEK 900.
- Cost of treatment by a doctor in primary care: SEK 2000.
- Cost of one day's inpatient care: SEK 8000.
- Cost of vaccine and administration of vaccination for one person: SEK 300.

For all scenarios, the SEK 300 vaccine costs are based on the assumption that the entire population is vaccinated (a total of 18 million doses), split evenly between vaccine cost and vaccine administration. This means that no savings on vaccine administration can be attributed to a lower number of vaccinated than 90%. The model presupposes absent workers to take care of sick children, and thus sick children do not produce the SEK 900 cost in a family where a parent is already ill.

3.3)Preliminary Method(with medium level of infectious)

Simulation starts in early June 2009, and after day 150 (early October) goes more intensive.

The following scenarios were compared: no policy response, school closure and vaccination (coverage 90%, 70%, 50%, or 30%). Each simulation covered 300 days and began with 50 randomly selected individuals infected on day 0. Each scenario was simulated ten times with different random seeds to obtain robust results and to examine variability. In all scenarios, children under three years and individuals over 70 years old were vaccinated first. Vaccination started after 100 days (in September). The doses were delivered weekly at a rate that gave all people time to be vaccinated with two doses over 14 weeks.

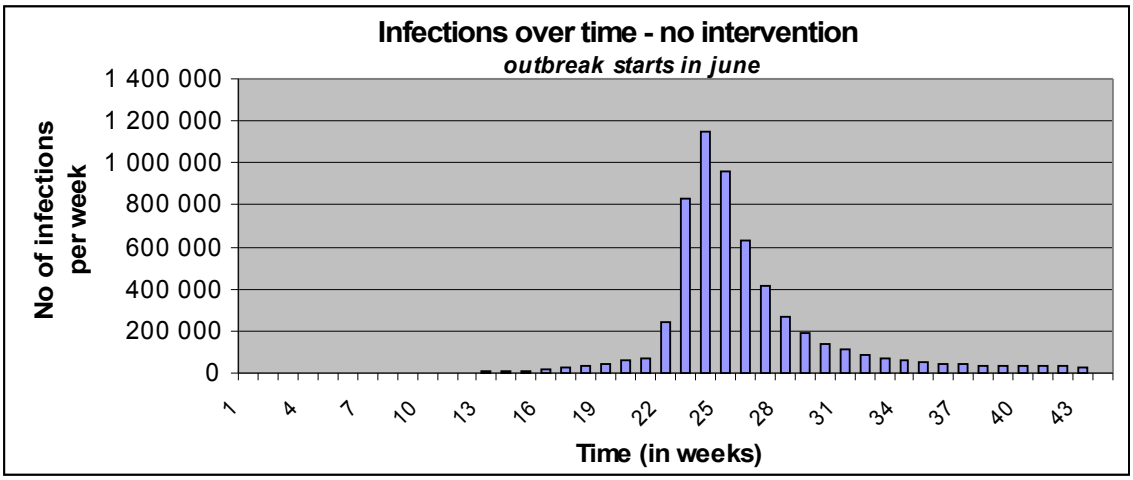


Figure 3.1. The number of infected persons per week during a simulation carried out without any countermeasures. [L. Brouwers]

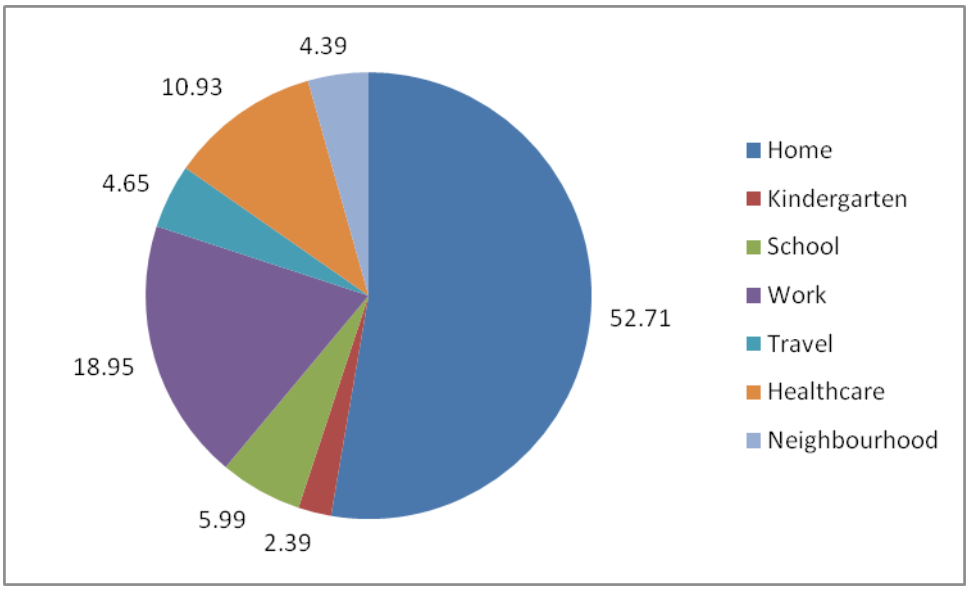


Figure 3.2. The place distribution of infected individuals, for the scenario without policy intervention. Numbers denote percentages. [L. Brouwers]

In Table 3.1, the total number of infected individuals are presented, averaged over ten runs (with a very low variance). In Figure 3.3, the age distribution for these ten runs is presented. This distribution is largely consistent with reports from actual spread, with an over-representation of the youngest (7.04019% infected versus a 5.28942% proportion of the Swedish population) and an under representation of the oldest individuals (6.0917% vs. 17.2947%).

Scenario	No. of infected
No intervention	5 787 064
School shut-down	5 737 835
Vaccination 30%	4 690 660
Vaccination 50%	3 672 291
Vaccination 70%	2 949 752
Vaccination 90%	2 912 569

Table 3.1. The total number of infected individuals, averaged over ten runs, for the six scenarios. [L. Brouwers]

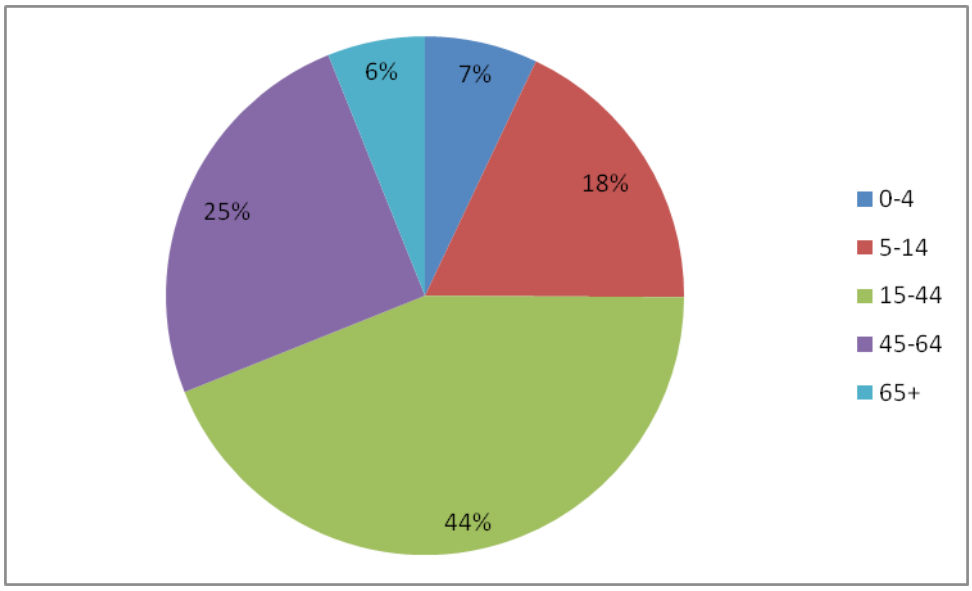


Figure 3.3. The age distribution of infected individuals. [L. Brouwers]

The costs (Figure 3.4 and Figure 3.5) result from a single full simulation per scenario, and should be interpreted as indicative only, but the current analysis points towards a 70% vaccination level as optimal, albeit with a very small difference to the 90% level. Society saves SEK 10 billion by vaccinating at least 70% of the population, mainly through reduced sick leave. The experiments indicate only small stochastic variations, but these may still prove important for the outcome and are subject to sensitivity analysis.

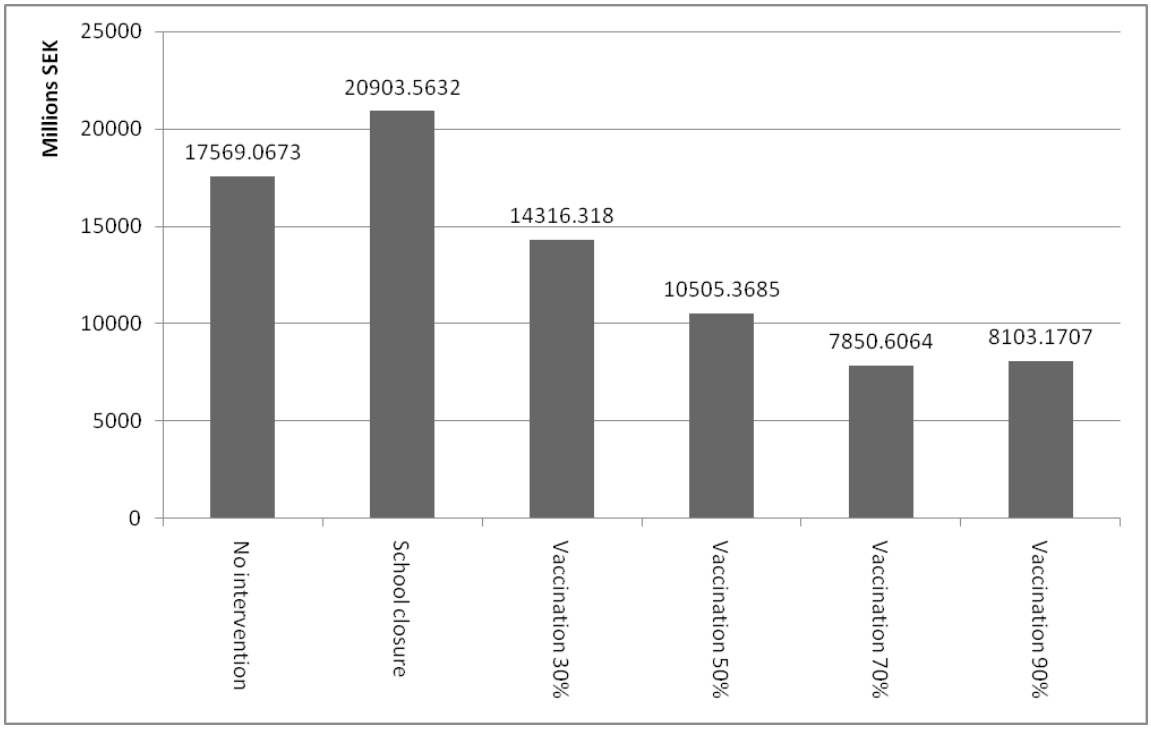


Figure 3.4. Total costs for the six scenarios. Results based on one full simulation. [L. Brouwers]

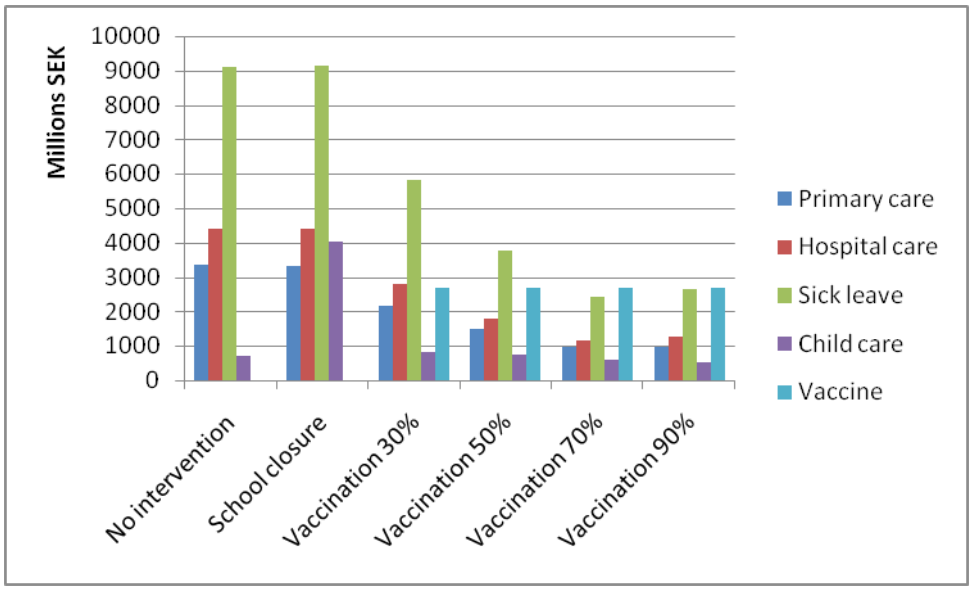


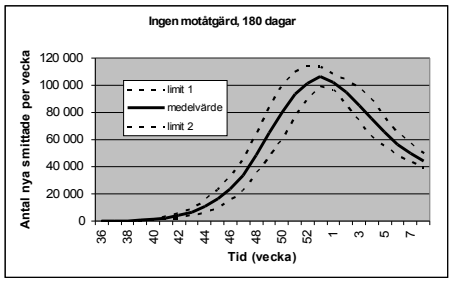
Figure 3.5. Costs broken down into their five constituents, for the six scenarios. [L. Brouwers]

3.4)Realistic Method(with low level of infectious)

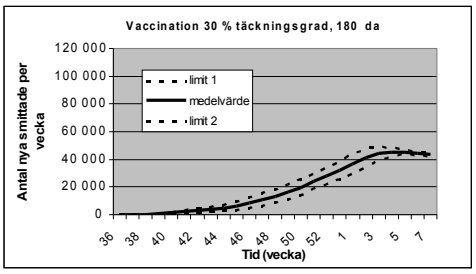
The following scenarios were compared: no response, the vaccination coverage of 30%, 50%, 60%, 70% or 90%. Each simulation take 180 days and starts with 50 randomly selected infected individuals at day 0. Day 0 in the model corresponds to the first September 2009. Some scenarios were investigated during 300 days, this was where it was interesting to see whether the outbreak was going to appear after 180 days.

- No intervention
  - 5 * 180 days
- Vaccination 30 %
  - 2 * 180 days
  - 3 * 300 days
- Vaccination 50 %
  - 7 * 180 days
  - 3 * 300 days
- Vaccination 60 %
  - 10 * 180 days
- Vaccination 70 %
  - 10 * 180 days
- Vaccination 90 %
  - 5 * 180 days

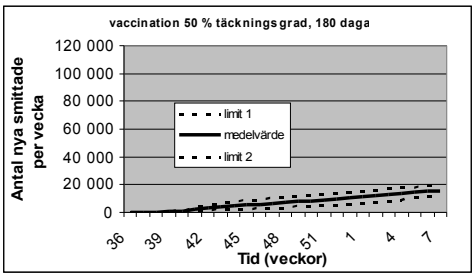
For scenarios 50%, 60% and 70%, it was deemed appropriate to carry out 10 experiments while 5 experiments were considered sufficient for the other. Extreme scenario with 90% coverage and 30% ratio is considered less likely as the rest of my scenarios (50%, 60% and 70%) why only 5 simulations were carried out by them. In total, 45 simulations carried out. School closure wasn't taken into account at all.



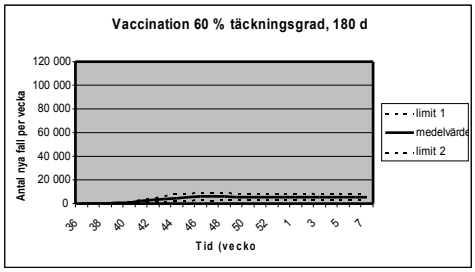
Picture 1. no intervention



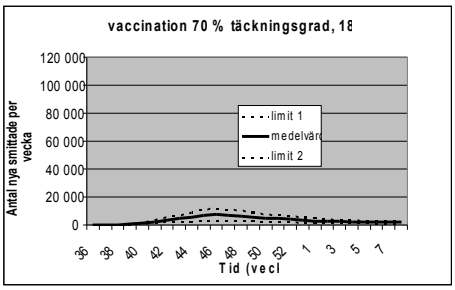
Picture 2. 30 % vaccinations



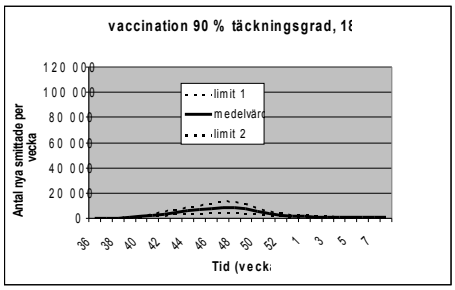
Picture 3 . 50 % vaccinations



Picture 4. 60 % vaccinations



Picture 5. 70 % vaccinations.



Picture 6. 90 % vaccinations.

Figure 3.6. Numbers of infections versus time for diffrent scenarous in six pictures. [L. Brouwers]

For that assumptions vaccinating decrease a lot number of infections (compare Figure 3.6 as time series and Figure 3.7 in total). That model were calibrated to influenza's epidemics from last years.

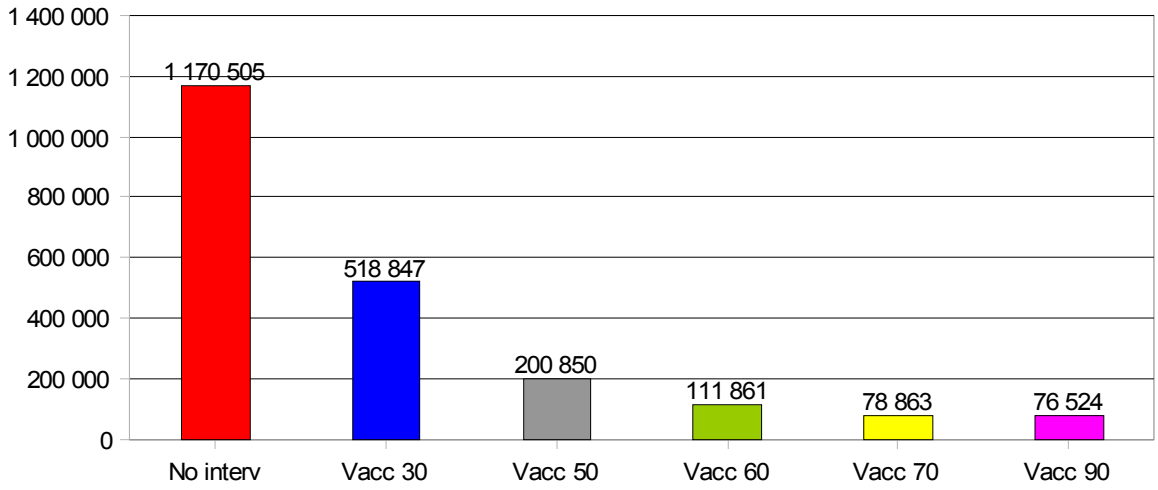


Figure 3.7. No of infections [L. Brouwers]

The most important for that analyze are costs. We were using the same approximation to establish real cost like in preliminary method. One more assumption was given to take in consideration cost of death cases. We used very small rate of death – 0,05% (because we have no idea how dangerous can be that in reality) so we underestimated that. The cost model used is simplified in several important respects. Firstly, neither direct nor indirect costs for the deceased are included. Since the case fatality rate for pandemic H1N1 influenza is still unknown one way to proceed is to use the best estimate, e.g., the 0.6% rate computed by Vaillant[14] from the reported deaths as per 16 July 2009.

The report made two runs, with and without death costs. A quantification of the socioeconomic burden of road deaths says National Institute for Transport and Communications Analysis, SIKA, in its report of 2008[15]. Identifies 22 million crowns as recommended score, so we used that.

	No interv	Vacc 30	Vacc 50	Vacc 60	Vacc 70	Vacc 90
PRIMARY_CARE	631 916 800	244 856 800	84 049 800	44 787 400	33 495 800	30 037 200
HOSPITAL	865 848 000	339 136 000	114 592 000	61 012 800	45 468 800	41 356 800
ABSENT ADULTS	1 815 908 160	648 611 520	215 486 640	114 739 680	86 782 680	82 300 080
HOME_WITH_SICK_CHILD	591 584 640	276 385 440	104 185 680	58 706 040	44 854 800	37 502 880
VAC	0	2 700 000 000	2 700 000 000	2 700 000 000	2 700 000 000	2 700 000 000
DEATH (0.05 % death risk)	585	259	100	56	39	38
Cost of deaths	585 252 700	259 423 600	100 425 143	55 930 650	39 431 617	38 261 800
Summ	4 490 510 300	4 468 413 360	3 318 739 263	3 035 176 570	2 950 033 697	2 929 458 760
Excluding deaths(gain)	**0**	**-674 356 120**	**164 988 360**	**367 499 910**	**425 691 690**	**442 138 180**
Including deaths(gain)	**0**	**22 096 940**	**1 171 771 037**	**1 455 333 730**	**1 540 476 603**	**1 561 051 540**

Table 3.2. Cost of influenza based on different issues [L. Brouwers]

14 Vaillant L, et al/ Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. 2009
15 http://www.sika-institute.se/Doclib/2008/PM/pm_2008_3.pdf [active on 01.2010]

As a summary should we conclude, that there is no sense to vaccinated only 30% of society. Even in incl. death cases gain is small, but in excl. death cases there is a lost.

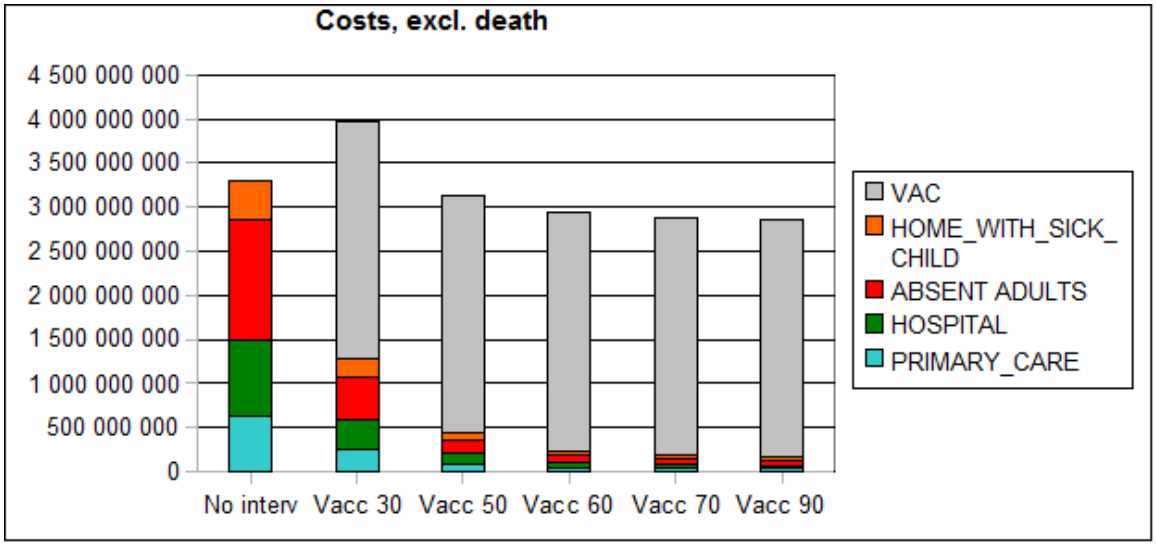


Figure 3.8. Total cost of influenza excluding cost of death cases in SEK [L. Brouwers]

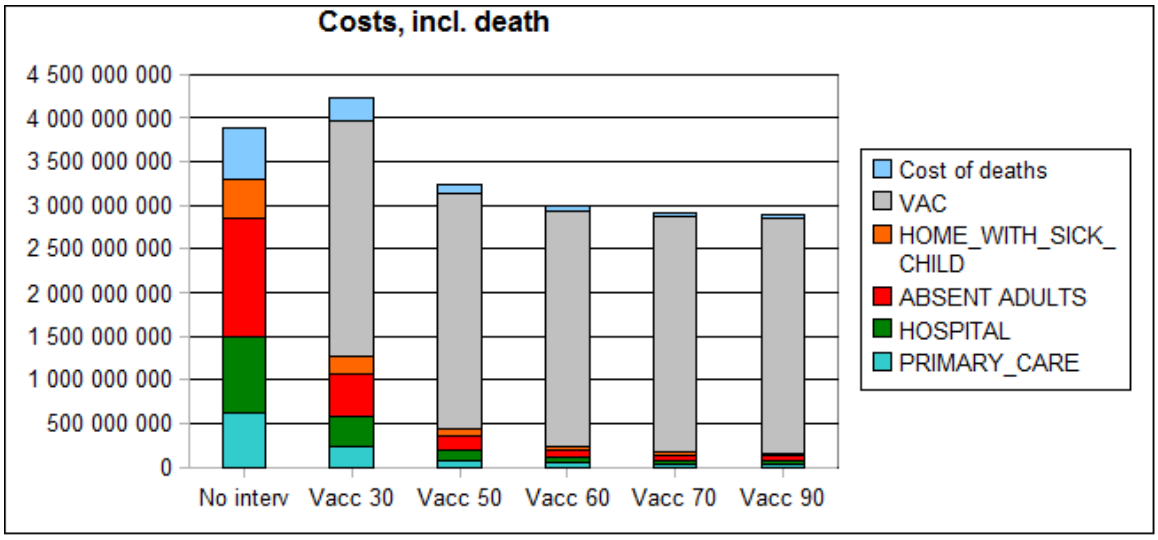


Figure 3.9. Total cost of influenza including cost of death cases in SEK [L. Brouwers]

In Figure 3.8 and 3.9 are very big costs of vaccinating. That state a question if vaccinating is really needed. In next method we assume less fortune scenario- if epidemic really appear.

3.5)Medium Method (with medium level of infectious)

Simulation was made on the same 45 part like in previous model, but in effect of shifted time (We took preliminary model without calibration and run simulations with shifted start time – 01.09 and start point of vaccination at 01.10) and lower immunity there appear much more infections. In comparing with low level we can see, that vaccination is not so effective as in low case (Table 3.3 and Figure 3.10)

		No interv	Vacc 30	Vacc 50	Vacc 60	Vacc 70	Vacc 90
Low 180	**Infections(mean) 180 days**	**1170505**	**518847**	**200850**	**111861**	**78863**	**76524**
	Gain	0%	56%	83%	90%	93%	93%
	Std	45345	63742	81440	52219	45586	37307
Low 300	**Infections(mean) 300 days**		**912078**	**448705**			
	Std		25842	40653			
Medium 180	**Infections(mean) 180 daysr**	**4617529**	**3309023**	**2825427**	**2672702**	**2589025**	**2577551**
	Gain	0%	28%	39%	42%	44%	44%
	Std	38081	16919	93479	120790	126918	176416
Medium 300	**Infections(mean) 300 days**		**3612653**	**2934285**			
	standardavvikelse		49149	59414			

Table 3.3. The total number of infected individuals, averaged over runs, for the different scenarios and methods and number of days in simulation. [A. Jarynowski]

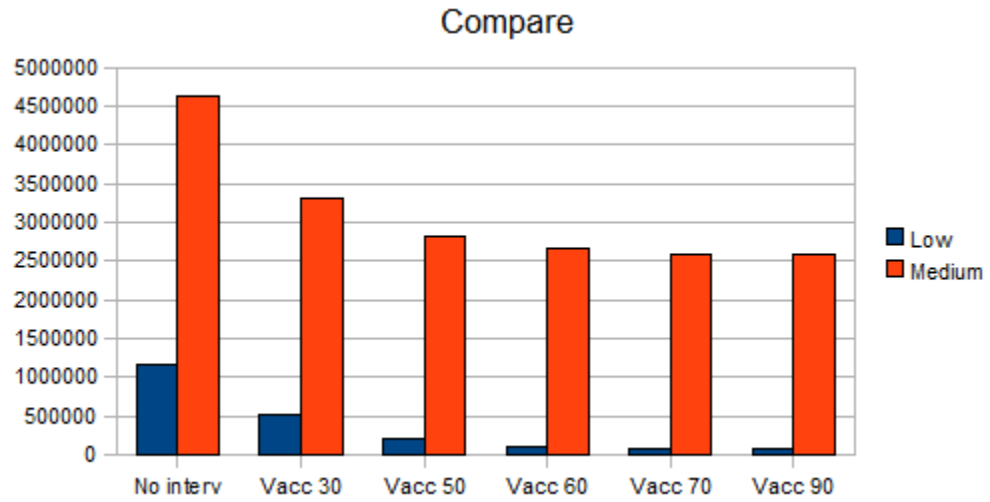


Figure 3.10. No of infections in both simulations low and medium [A. Jarynowski]

cost	PRIMARY_CARE	HOSPITAL	ABSENT ADULTS	HOME_WITH_SICK_CHILD	VAC	sum
no	2139230400	2871616000	5788796220	757613340	0	11557255960
30	1686394400	2263432000	4494766680	790126380	2700000000	11934719460
50	1213502800	1633878400	3262724280	656091270	2700000000	9466196750
60	1102235800	1486430400	3003084630	598650570	2700000000	8890401400
70	1059860600	1428322400	2909138040	560117970	2700000000	8657439010
90	1122042800	1509398400	3123631080	510083460	2700000000	8965155740

Table 3.4. Cost of influenza based on different issues [A. Jarynowski]

For that more dangerous scenario we can see that cost of vaccinating is not so big as other issues(even that death cases wasn't include in consideration)

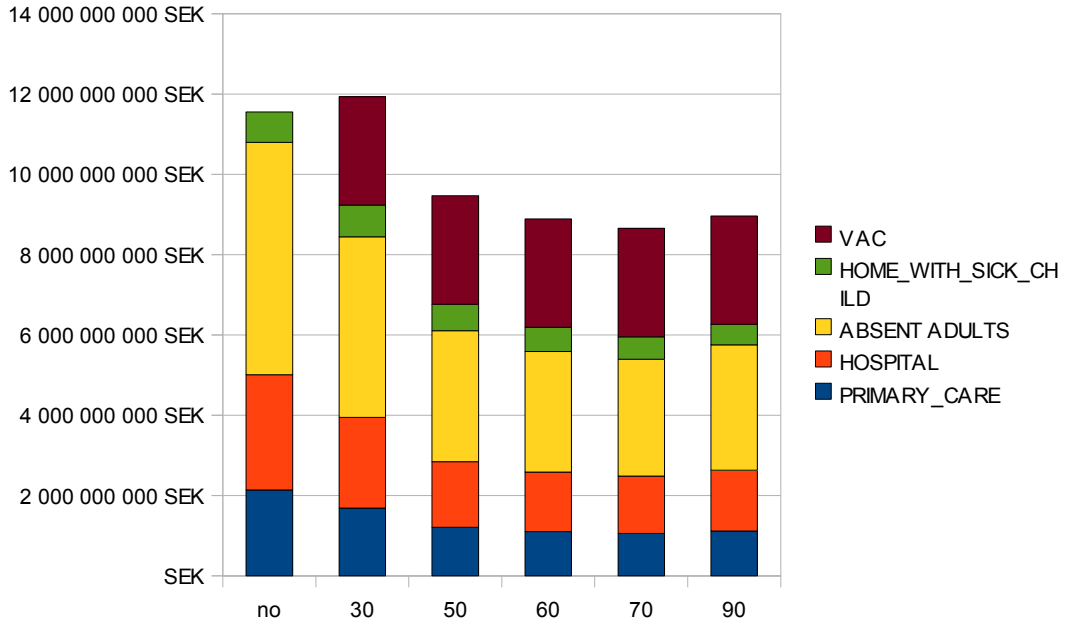


Figure 3.11. Total cost of influenza excluding cost of death cases in SEK [A. Jarynowski]

3.6)Discussion

This model is one of the first[16], which are using individual social properties of society and it is first one, which works on scale of whole country. We have to careful with interpret the results. It was announced to the media and if You look at official report, You will find that it was censored to avoid public panic. One thing is very important-Swedish politics makers have seen it and they gave feedback, which make this model more realistic. One of conclusion of the report was to vaccinate more than 70% of population. In Sweden, vaccination is voluntary, but for the purpose of these simulation experiments it was assumed, somewhat unrealistically. A recent survey, conducted on behalf of the National Board of Health and Welfare, on attitudes towards vaccination in Sweden, found a 72% willingness-to-vaccinate. The survey was conducted between July 27 and August 23, and consisted of 2,000 interviews. It is difficult to say when appear really outbreak, but when we look at real data we can see, that model is almost correct to this time with following suggestions: Authors hypothesis is that the relatively rapid, especially in view of the R0 values reported, peaks in Australia and New Zealand could be explained by the earliest cases going unrecognized, and a constant influx of new cases from abroad.

16 Brouwers L, Camitz M, Cakici B, Mäkilä K, Saretok P. MicroSim: modeling the Swedish population.

4)Cellular Automata

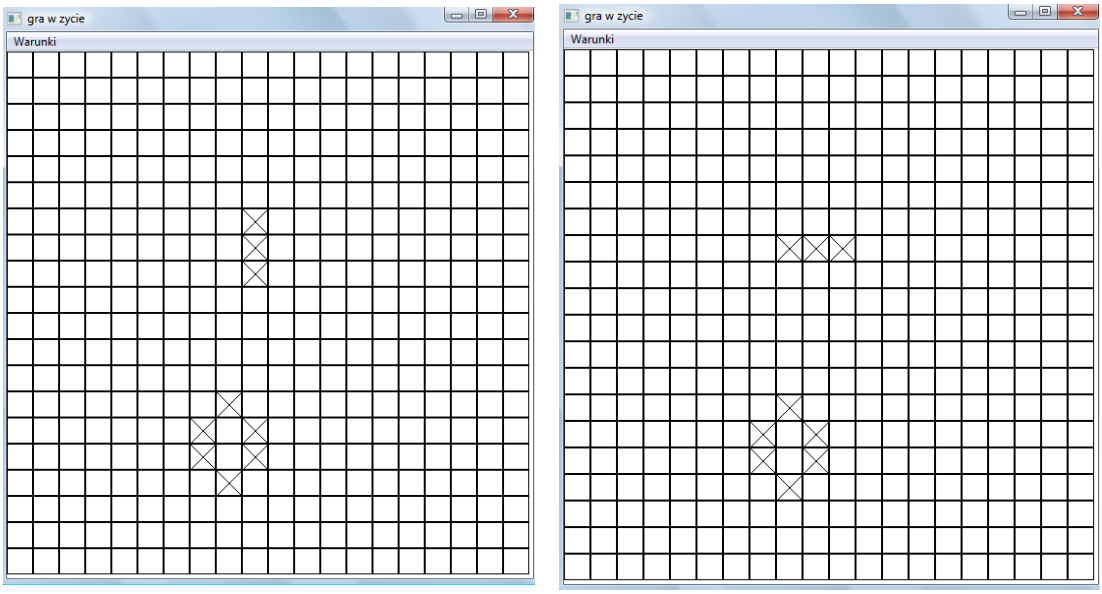
4.1)Introduction

Cellular Automata were invented in early 50th. There based on some designed topology of elements which have some possible number of states and they can evaluate in time. A cellular automaton may be also a collection of "colored" cells on a grid of specified shape that evolves through a number of discrete time steps according to a set of rules based on the states of neighboring cells[17]. In addition to the grid on which a cellular automaton lives and the colors its cells may assume, the neighborhood over which cells affect one another must also be specified. The simplest choice is "nearest neighbors," in which only cells directly adjacent to a given cell may be affected at each time step. Two common neighborhoods in the case of a two-dimensional cellular automaton on a square grid are the so-called Moore neighborhood (a square neighborhood) and the von Neumann neighborhood (a diamond-shaped neighborhood). One of the most famous is „Game of life" introduced by J. Conwey. To illustrate how it can look like we wrote program. It called „Gra w życie *(Game of life)*". We proposed 2 screen-shots, which representing two time steps. The rules can be described in two-dimensional grid with possible state, live or dead. and with the von Neumann type neighborhood:

1. Any live cell with fewer than two live neighbours dies, as if caused by underpopulation.
2. Any live cell with more than three live neighbours dies, as if by overcrowding.
3. Any live cell with two or three live neighbours lives on to the next generation.
4. Any dead cell with exactly three live neighbours becomes a live cell.

The initial pattern constitutes the *seed* of the system. The first generation is created by applying the above rules simultaneously to every cell in the seed—births and deaths happen simultaneously (let look at picture 4.1 and You can find seed situation on left and first step on rigth). The rules continue to be applied repeatedly to create further generations. Colony can by static (like in the middle of picture 4.1) or dynamic ((like on top of picture 4.1)

17 Wolfram, S. *A New Kind of Science.* (2002)



Picture 4.1. Screen-shots from my program "Game of life 2005": example of cellular automata [A. Jarynowski]

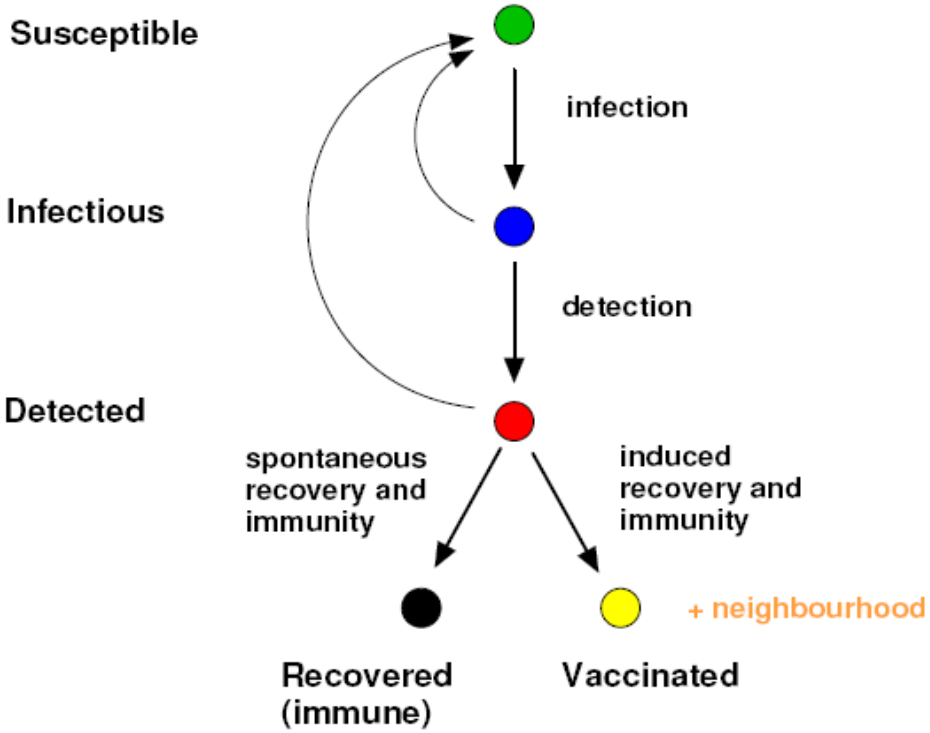
4.2)SIR

Computer simulations of cellular automata are considered as one of possible methodologies for investigation of epidemiological models. The main goal of those investigations is a statistical analysis of the SIR model of the epidemic spread with accumulated exposure. We would like to propose some simple but powerful models. At the beginning there are some assumptions.

Individuals are placed on a given topology and can be in one of the following states:
1. *S* – susceptible (or healthy), which can be infected with probability p by any infectious or detected individual in its epidemic neighborhood;
2. *I* – infectious (infected but pre-symptomatic); can infect other nodes from its epidemic neighborhood but cannot trigger a control measure. In addition, with probability q it can spontaneously move to the detected class, i.e. symptoms become observable;
3. *D* – detected (infected and symptomatic), can infect other nodes from its epidemic spread neighborhood. In addition, it can spontaneously move to the recovered class (with the probability r) or can trigger a treatment measure with the probability v that includes all individuals within its control neighborhood;

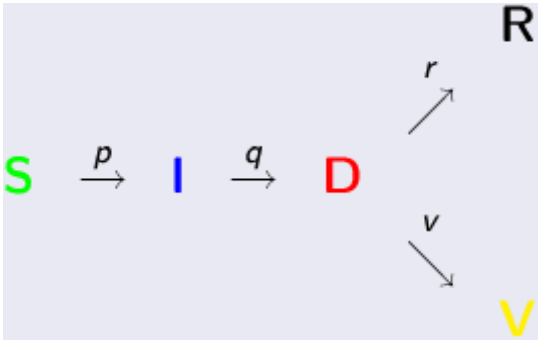
4. *R* – recovered. This class includes individuals that have been through the disease, can be treated but cannot become re-infected;
5. *V* – vaccinated (treated). Individuals in this class have been in a control neighborhood of a detected individual when the treatment event was triggered. They cannot become re-infected.

Elements of the simulation environment:
-possible transition states of individuals
-structure of the interaction topology
-costs (eg $X = R\ (inf) + V\ (inf)$), where total cost is based on cost of treating infections (*R*) and cost of socio-political intervention like vaccination (*V*)



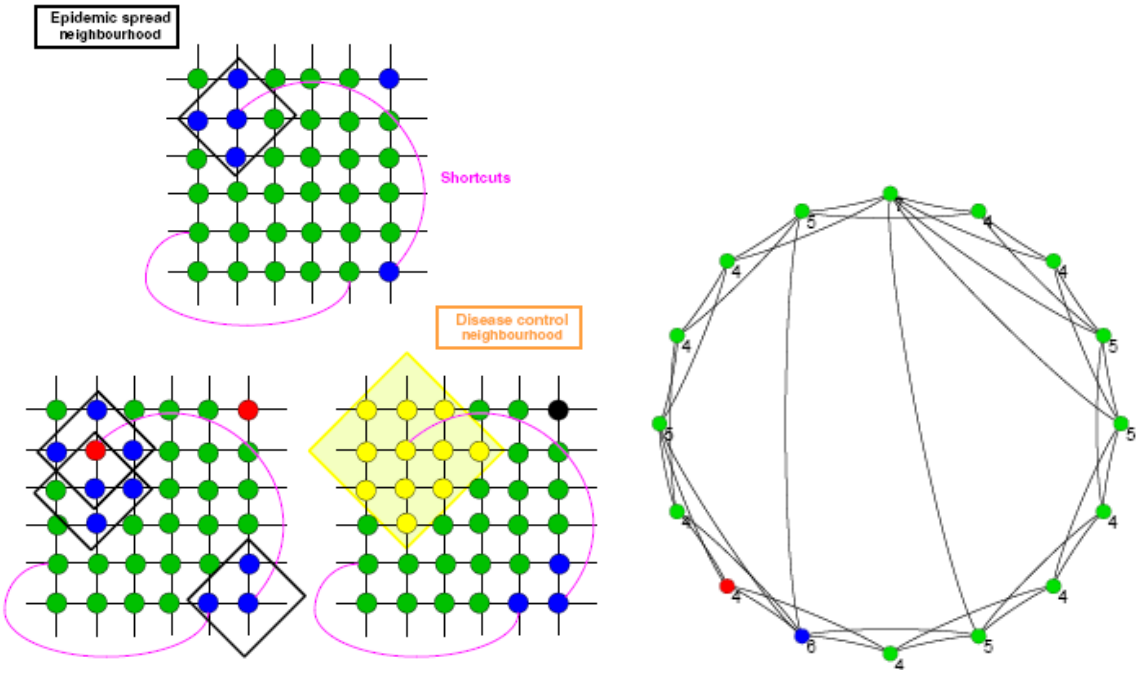
Picture 4.2. Schema of changing states [B. Dybiec]

As usually main goals of epidemiological modeling is to provide guidelines for controlling disease outbreaks. Dybiec has proposed a strategy that is a mixture of responsive and preventive actions. Method is vaccinating neighbors of infected element.



Picture 4.3. Schema of transition infection [B. Dybiec]

The first approximation is to study static 2D with von Neuman neighborhood. In real life we have much more complicated topology, so I'll present 2 proposition: Small World topology[18] and jumps[19].

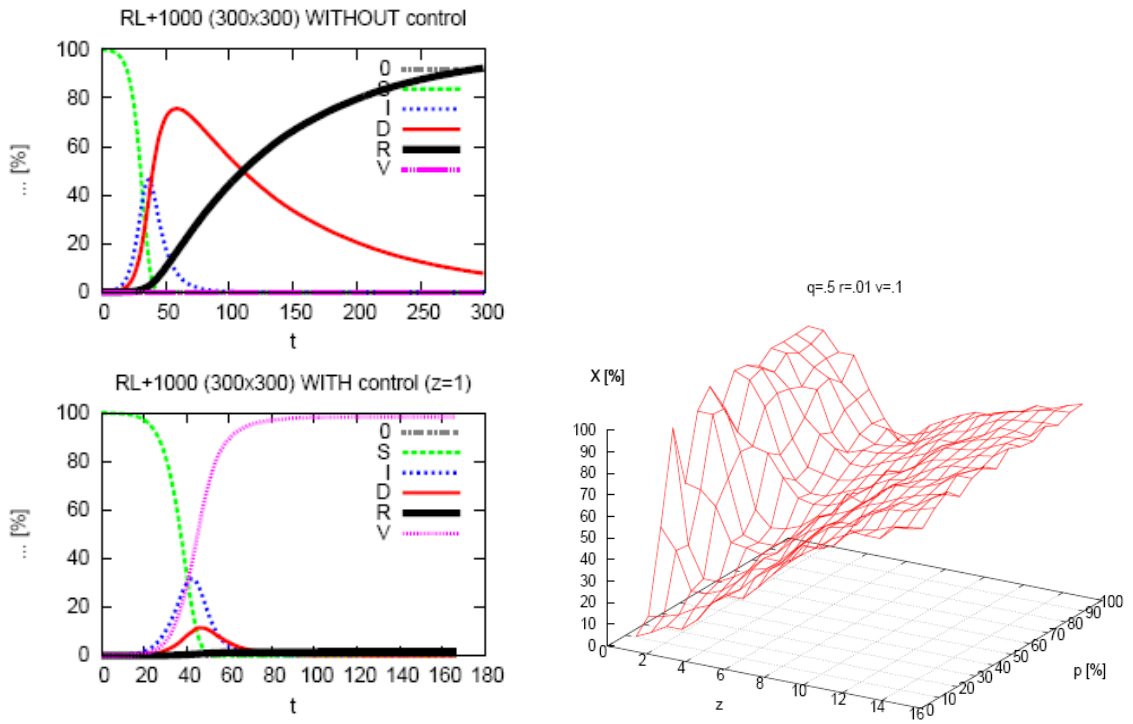


Picture 4.4. (left-a)How changes of topology develop epidemiology model (right-b), Visualization of small world topology [B. Dybiec]

18 " Economic and social factors in designing disease control strategies for epidemics on networks", B. Dybiec, et al. (2006)

19 "SIR model of epidemic spread with accumulated exposure", B. Dybiec (2009)

Usually people contact not only with neighbors (like in classical 2D lattice), but also with others-away (on picture 4.4a that contact is a shortcut and on picture 4.4b is lines crossing that circle). A small world network, where nodes represent people and edges connect people that know each other, captures the network. The most important element of control is vaccination. Parameter *z*-is a radius of vaccination.

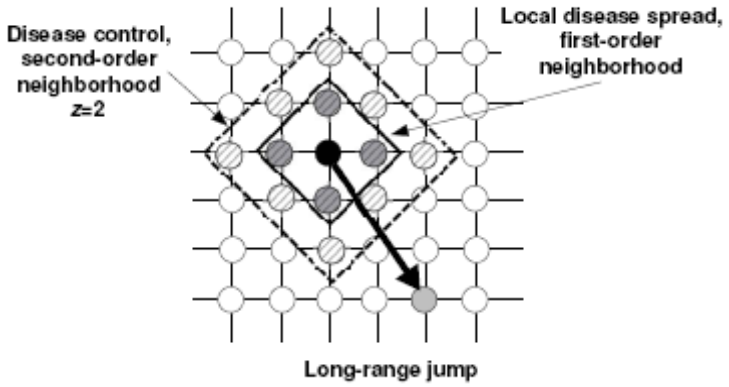


Graph 4.1. (left-a) Time evolution with and without control (right-b), Total cost of epidemic depend on vaccination radios and intensivity of disease. [B. Dybiec]

We can see from the graph 4.1b that there is the optimal radius of vaccination.

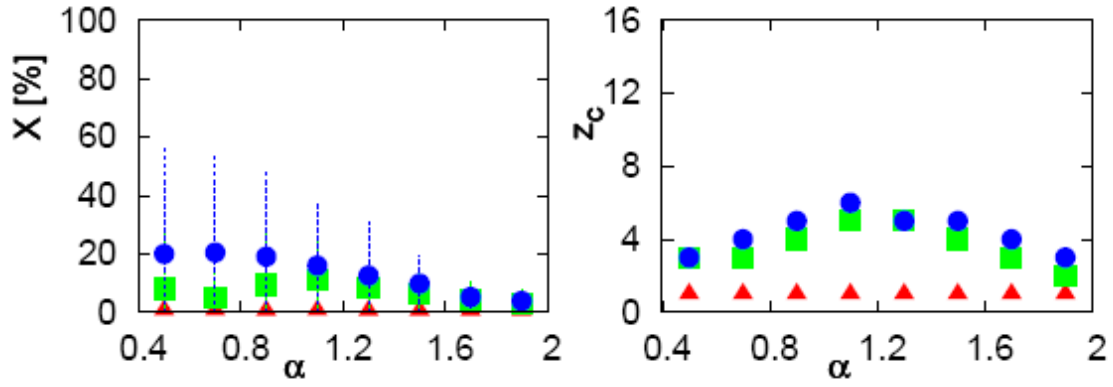
Second method of making model more realistic are jump There is possibility to change place on a lattice with some probabilities from specific long-tailed distributions like α-stabile[20].

20 A. Janicki, A. Weron, Simulation and Chaotic Behavior of α-Stable Stochastic Processes (1994)

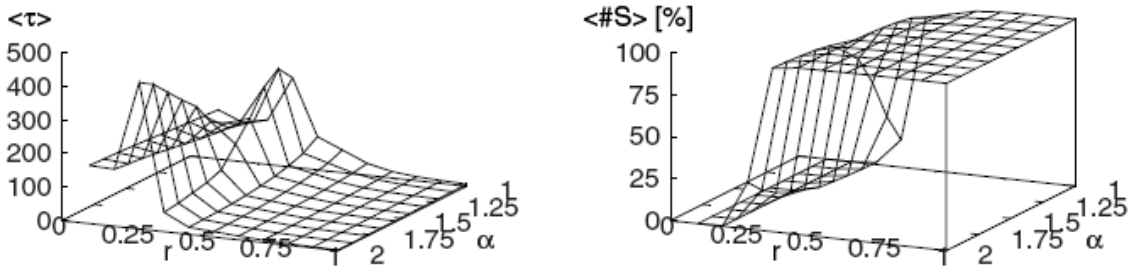


Picture 4.6. How allowing jumps develop epidemiology model [B. Dybiec]

Vectors-jumps are valid globally, so bigger variety (smaller α) make bigger cost (look at the graph 4.2a). On the other hand for medium variety (medium α) the optimal radius is the biggest (graph 4.3b and 4.4a)



Graph 4.2. (left-a) Total cost of epidemic depend on α. (right-b) Critical radios of vaccination depend on α.[B. Dybiec]



Graph 4.3. (left a) Average duration of the epidemic, τ and (right b) average number of individuals in the susceptible state, $\#S$ at the end of the epidemic as a fraction of the total number of individuals. [B. Dybiec]

Cellular Automata could explain few more question than differential equations, but there are not so powerful as pure agent-based model with more realistic topology, which I presented in chapter 3.

5)Contact networks and the spread of MRSA in Stockholm hospitals

5.1)Introduction

In recent years, the knowledge of social networks experienced an accelerating growth. To solve more complex and sophisticated social problems, new types of tools and models are constantly developed. Mathematical models and computer simulation start to play more significant role as quantity of social interactions is enormous. For sociology simulation[21] modeling is very important because it provides the insight into the dynamics of the social process whereas commonly used methods of research not always make it possible. Moreover, such models allow not only to test theory but also they are inspiring and may support constructing new theories in sociology. The most interesting is the possibility to study the dynamics of collective behavior itself and the relationships among variables of interest. More important than simulations are real data especially register-based. Simulation has sense only if there are some data you can calibrate parameters to run yours simulations. This need enables cooperation between registering institutions which exerts a pressure on collecting data for simple analyze with many researchers who work on new models and use complex tools taken often from other disciplines. I'll be coupling with epidemiological data.

5.2)Background and social network

The bacterium meticillin resistant Staphylococcus aureus (MRSA) is resistant against more than half of all antibiotics sold in Sweden. MRSA is known to alone be the largest care related the infection problem. The Nordic countries, together with Holland and Great Britain, were for long spared from MRSA. During the 1990s, however, the number of infections increased rapidly. During approximately four years, the number of MRSA cases grew drastically in Great Britain, who now has the same high levels of MRSA as the U.S and continental Europe. No British countermeasures seem to succeed in hindering

21 "Opinion evolution in closed community", K. Sznajd-Weron, J. Sznajd, (2000)

this development. In the end of the 1990s, Sweden was hit by MRSA outbreaks in the healthcare sector in the city of Göteborg. A national MRSA spread was avoided thanks to efficient counter measures which were very costly and cumbersome. Since the year 2000 there has been one MRSA outbreak in the healthcare sector in Stockholm [22](Stenhem et al 2006). It would be very problematic if MRSA was established in Stockholm hospitals; it would imply high costs to cover for increased care needs and also impose an infection risk for the patients, similar to the evolution seen in Great Britain. MRSA would also become a big work environment problem, since healthcare personnel has a key role in the spread of MRSA. The carriers mainly have the MRSA bacterium on their skin. Especially places where the skin is damaged, like eczemas and wounds, are places where the bacterium can grow and replicate fast. MRSA is spread through direct or indirect skin contact between people. For diseases like MRSA, where the contacts must be close for a transmission to take place, it has been showed that the social network structure impacts the course of the epidemic[23] . It has for instance been shown that it is easier for a disease to become endemic in a population if there is a large variation in the number of social contacts[24] If persons in the population tend to have contacts with persons who have the same number of contacts as themselves, the risk for an outbreak is increased. Sharing contacts with their contacts in a population has a limiting effect on the outbreak on the other hand. For less infectious diseases, where a close contact is needed for a transmission to occur, the individual's position in the contact network is important for the person's risk to get infected. The awareness of the importance of contact network has brought methods from sociological studies of social networks into the area of preventive infectious disease protection work, for instance sexually transmitted diseases and tuberculosis. Today, the term network epidemiology has become an established concept within infectious disease epidemiology.

22 "Epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) in Sweden 2000-2003, increasing incidence and regional differences." M. Stenhem,2006

23 Sexual networks: implications for the transmission of sexually transmitted infections. F. Liljeros, *Microbes and Infection 2003*

24 R. Anderson *Infectious diseases of humans 2003*

Picture 5.1 An example of two different contact networks where the average number of contacts per individual is equal, but where the structure of the network provides different conditions for spread. The fact that individual C in the left graph has considerably more contacts than all other individuals makes an outbreak more likely (and has bigger influence on other prisoners) in this network than in the network to the right. Person C in the left network is also the individual who has the highest risk of becoming infected (and prison mates has the biggest chance for future with him). [F. Liljeros]

5.3)Question asked and dataset

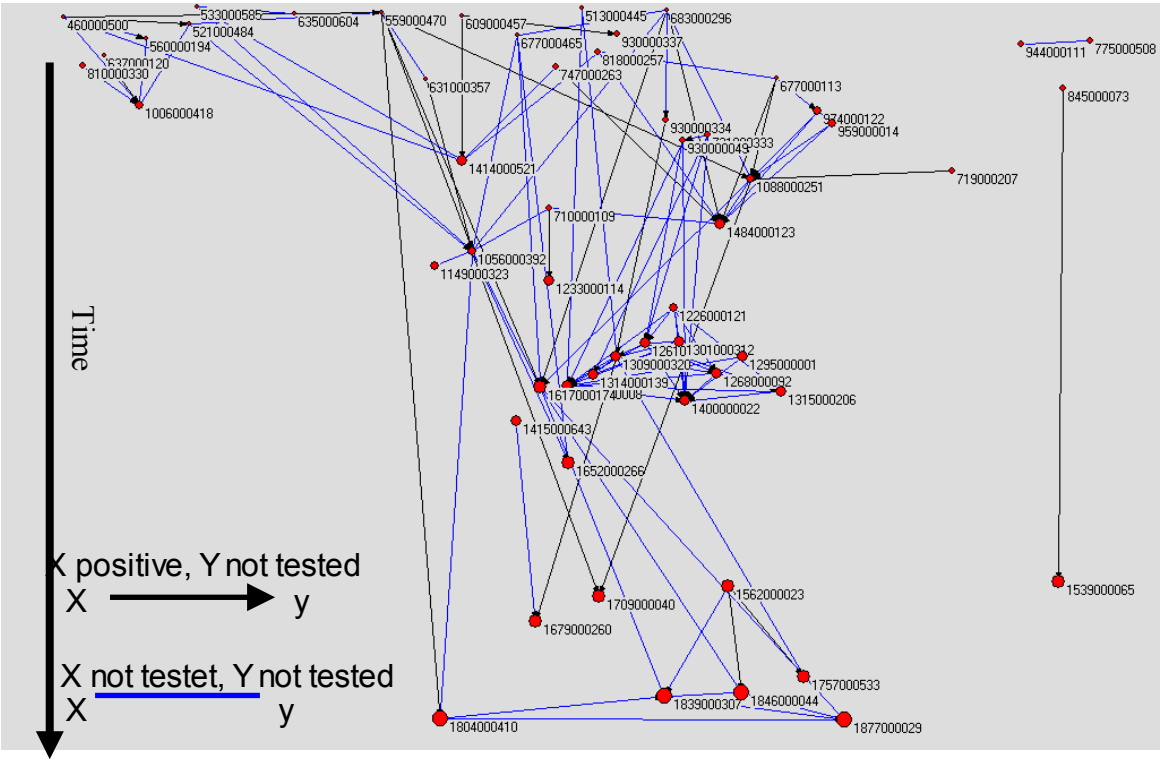
The aim of the current project is to increase the understanding of how MRSA is transmitted in Swedish hospitals. Methods to analyze the contact network of persons visiting the same care unit will be developed within the project as well as methods to analyze in what way network structure affects the transmission of MRSA.

- Is it possible to estimate transmission probabilities in contact networks based on empirical data on diagnosed cases and network data?
- Could these models help to localize unknown carriers (and spreaders) of MRSA?
- Are there properties in the patients' contact patterns or specific positions within the contact network that are correlated with a higher risk of being diagnosed with MRSA?
- Do different genotypes of MRSA display different transmission patterns in hospitals?

The project will use anonymized data from two linked healthcare registries; (1) the Common Care Registry (CCR) containing information about all in- and outpatient visits within Stockholm County during the period 2000-2006. The other dataset (2) is a registry over diagnosed MRSA cases in Stockholm County during 1999-2005. CCR holds information on care unit and time and date for all entries and discharges within the inpatient care. It also contains information on unit and date for each outpatient visit.

Some facts:

- 1337 Cases
- Population 2 314 517 Patients
- 210 different types of MRSA
- UK-E15 is the most frequent one
- The outbreak is now under control

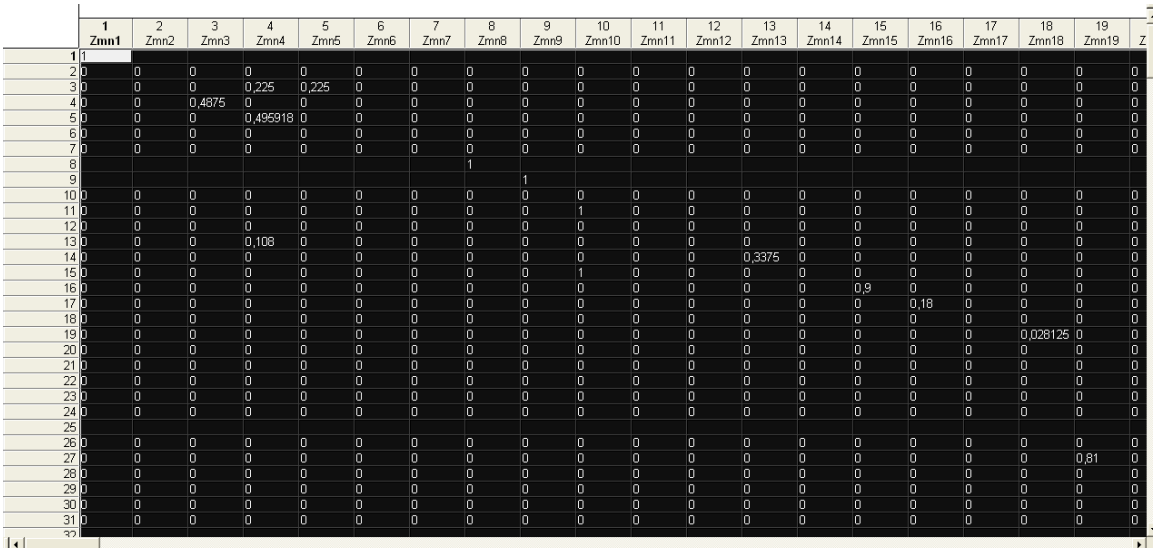


Picture 5.2 An example of several transmission paths in MRSA spreading. The most important thing is to know what probabilities is on the links. [pic. by F. Liljeros]

5.4)Main method of realization

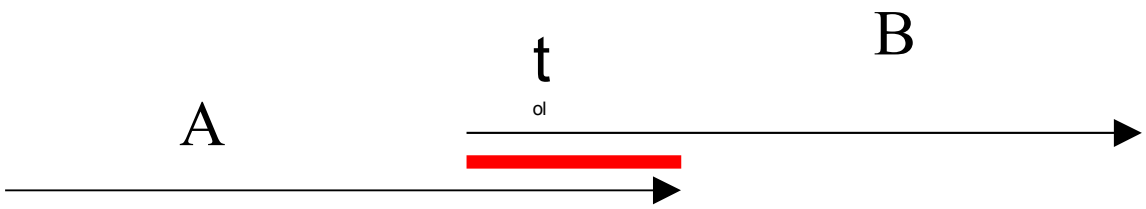
We study matrix of disease transition in hospitals population. This matrix is my first goal. In rows are Infected and in Columns people, who could sent infection. Elements of

matrix are probabilities, what Infection was sent by indicated person. Diagonal elements are probabilities of being infected by someone out of hospital, but they are in first approximation zeros. Unfortunately ¼ of all infected are patients, who had no contact with no other infected person.



	1 Zmn1	2 Zmn2	3 Zmn3	4 Zmn4	5 Zmn5	6 Zmn6	7 Zmn7	8 Zmn8	9 Zmn9	10 Zmn10	11 Zmn11	12 Zmn12	13 Zmn13	14 Zmn14	15 Zmn15	16 Zmn16	17 Zmn17	18 Zmn18	19 Zmn19	Z
1	1																			
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0,225	0,225	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0,4875	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0,495918	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8								1												
9									1											
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0,108	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0,3375	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,9	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,18	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,028125	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25																				
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,81	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Picture 5.3. Matrix for type 185. In rows are Infected (291) and in Columns people, who could sent infection (291 who also were infected). Elements of matrix are probabilities. In diagonals are sometimes 1-it means, that this patient was infected outside social network. Calculation of probabilities base on time of overlapping in the same ward shifted additionally with constants value, which is related to order of time of being infected(we have in our data only a date of testing positive for having MRSA). [A.Jarynowski]

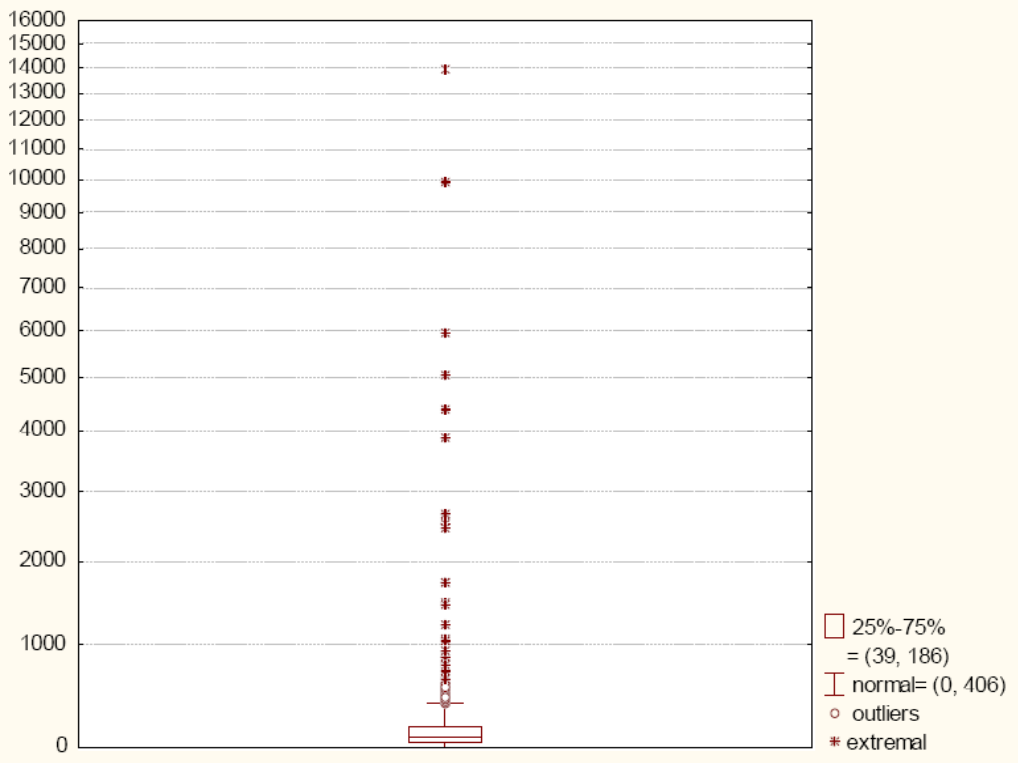


Picture 5.4 Probabilities calculation is based on time of contact. This is the same in epidemiology spreading (time of sharing the same warp or clinic-second order neighborhood) [F. Liljeros]

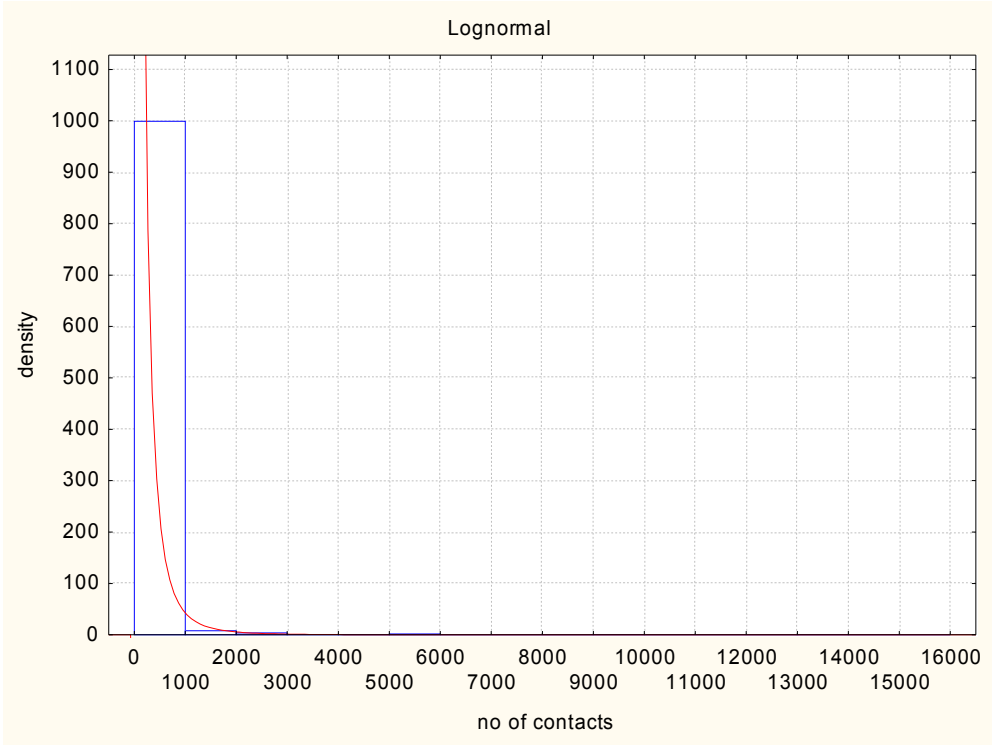
5.5)Stationary case

5.5a)Some statistical properties of hospital network

First view at data gave us some information, but their utility is low. There is a lot of problems with finding paths of transition disease. One of the most important is lack of knowledge of date of infection. In our dataset exist only a date of testing positive. That's mean, that we potential sender could be health or ill in contacts before his test. Firstly look at properties without taking this fact into consideration.

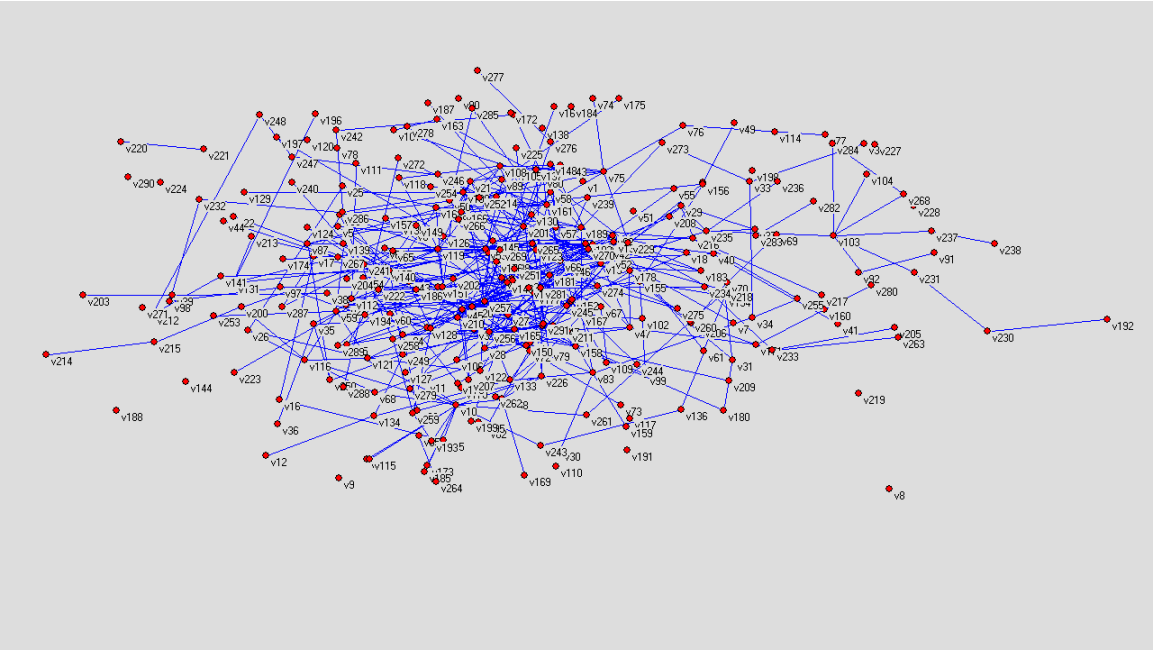


Graph 5.1. Scatter plot of number of contact ill persons with others. Most cases are between 39 and 186, but there are few outliers as well. [A.Jarynowski]



Graph 5.2. Density plot of number of contact ill persons with others. There is also a fit with lognormal distribution [A.Jarynowski]

As a conclusion we can say, that there are some patients, who were tested positive, who has huge numbers of contacts. Hospitals usually want to isolate potential MRSA spreaders (only 1018 from 1337 all ill patient have contacts with other patients and they who have contact with someone infected are 107351). That extremely contacted patient can be tread as a seeds of disease and I would like to focus on them in future. In type 185 there are no extremes ‘socialized’ infected.



Picture 5.5 Visualization of 291 cases of MRSA type-185 and their connections (Free energy method of presenting network). [A.Jarynowski]

5.5b)Test of influence to being infected

To show how difficult and unexpected is this problem in traditional statistical ways I propose statistical significant test. Our dependent variable is binomial (0-health, 1-ill) in case of MRSA and explaining variables are number of day spend with tested positive and number of visit in the same care unit in which tested positive was present. A statistical hypothesis test is a method of making statistical decisions using experimental data and in our case is it logistic regression as a joining function with result taken from {0,1}. The null hypothesis was that the visit and days have significant influence on being infected. The distribution associated with the null hypothesis was the binomial distribution. We have checked 3 models:

- with one explaining variable: only days or only visits
- with both explaining variables

In all cases p-Values of all explaining variables is above 0,1 so there is now significant dependence between explaining and dependent variables. Even that fact, when we look at evaluation of correlation we can see, that there is negative coefficient for days in all test. It means that, increasing number of days spend with infected conclude lover chance to being infected, what is unexpected. We don't know how to explain this paradox, but it is quit a lot below significant level. More important variable is sense of significant (because

p-Value is closer to 0,1) is number of visits in unit occupied by infected and coefficient is positive what is more intuitive.

Efect	binomial test values(ill-1 or health-0)			
	Evaluation	standard error	Wald Stat.	p
free element	-4,01480	0,025059	25669,39	0,000000
days	-0,00027	0,000486	0,31	0,579326

Efect	binomial test values(ill-1 or health-0)			
	Evaluation	standard error	Wald Stat.	p
free element	-4,03633	0,028881	19532,57	0,000000
visits	0,00866	0,009107	0,90	0,341506

Efect	binomial test values(ill-1 or health-0)			
	Evaluation	standard error	Wald Stat.	p
free element	-4,03273	0,029137	19156,58	0,00000
days	-0,00042	0,000528	0,64	0,42213
visits	0,01124	0,009544	1,39	0,23883

Picture 5.6. Results of statistical hypothesis tests. Free element is part of a model with does not depend on any variable and only this element is significantly important. [A.Jarynowski]

5.5c)Matrix of disease transition

We study matrix of disease transition in hospitals population. This matrix was my first goal. In rows are Infected and in Columns people, who could sent infection. Elements of matrix are probabilities, what Infection was sent by indicated person. Diagonal elements are probabilities of being infected by someone out of hospital, but they are in first approximation zeros.

We produced also matrixes for all Infected vs all Patient, and smaller matrixes for special types of MRSA. To correct matrix we propose shifting mechanism. It is changing probabilities using all knowledge we have: date of testing positive.

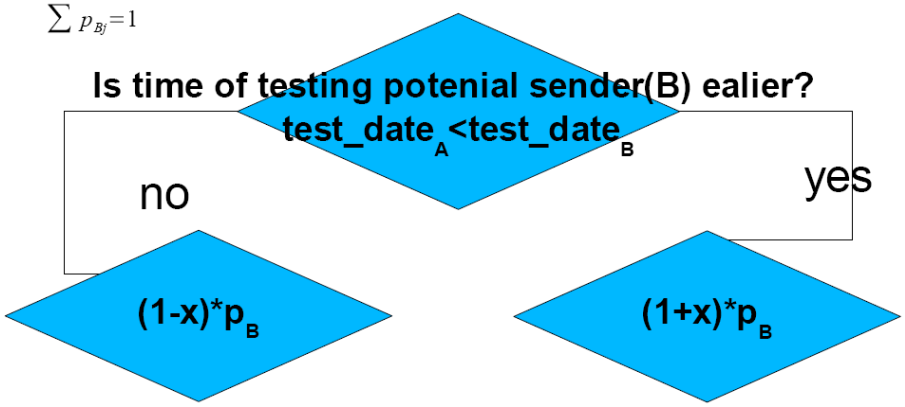
Let consider time of testing in potential sending MRSA (we do not know when exactly

people were infected) There are n-infected which are divided into different types of infection, and m-patients, so there are m-n not infected patients:

A-individual infected

B-set of all infected

p_{B1} – *B1->A* example for one potential sender where *j*=1



Picture 5.7. Schema of shifting probabilities [A.Jarynowski]

That process gives us better estimators of probabilities. Let assume x=0.1 In stationary case we have matrixes of probabilities, which does not depend on time. I have estimated it at about 25% (how many causes cannot be explained from infected-infected matrix)

	1 Zmn1	2 Zmn2	3 Zmn3	4 Zmn4	5 Zmn5	6 Zmn6	7 Zmn7	8 Zmn8	9 Zmn9	10 Zmn10	11 Zmn11	12 Zmn12	13 Zmn13	14 Zmn14	15 Zmn15	16 Zmn16	17 Zmn17	18 Zmn18	19 Zmn19
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	3,6	3,6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	11,7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	48,6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	27	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	5,4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	2,7	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,7	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1,8	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1,8	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16,2
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

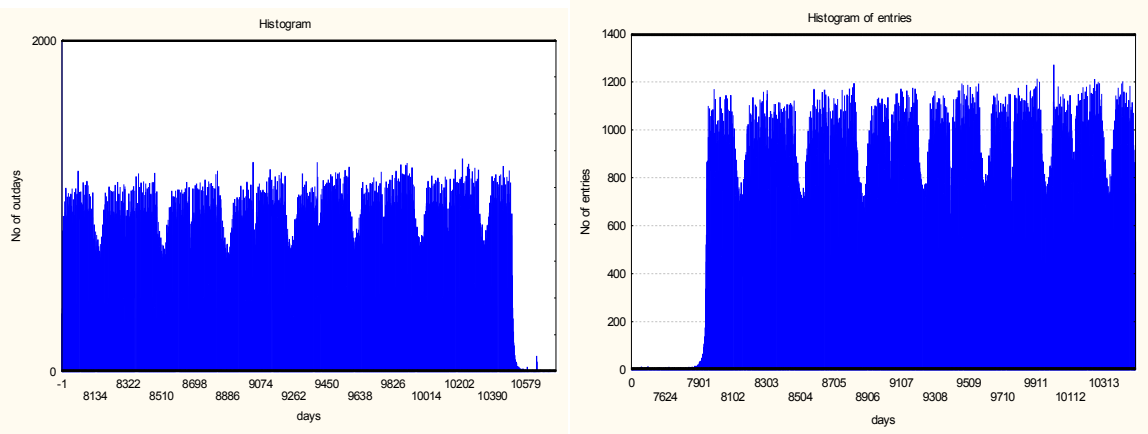
Picture 5.8. Matrix for type 185 (compare with Picture 5.1). Elements of matrix are not probabilities, but days spend in the same unit after shifting. In diagonals are 0. [A.Jarynowski]

5.6)Time evaluating case

5.6a)Real data analyze

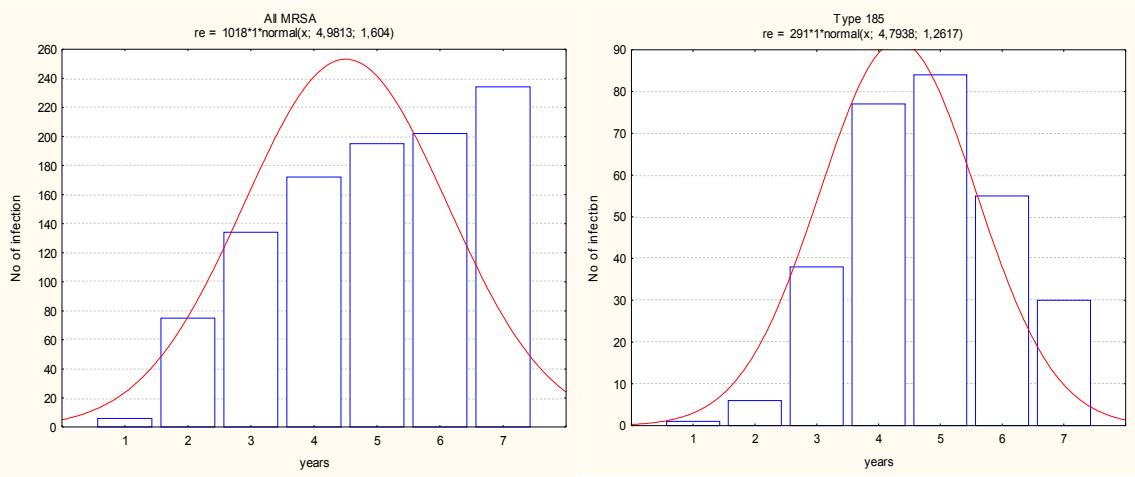
Let build matrixes of contacts in smaller times intervals (*dt*). Let starts from time t_0 (1999) and matrix P_0. That can divided The Stockholm Outbreak 1999-2005 into smaller periods, but last *P* will show situation during period (2005-*dt*). From that data we will also need matrix matrixes P' which won't be normalized and tell us some characteristics of numbers of contacts for patients in that time intervals (with contacts with also non-infected patients).

The best *dt* is whole year because of periodicity of visits to hospitals. That mean, that there will be 7 matrixes (both *P* and *P'*), in which we are considering contact networks in that time interval.



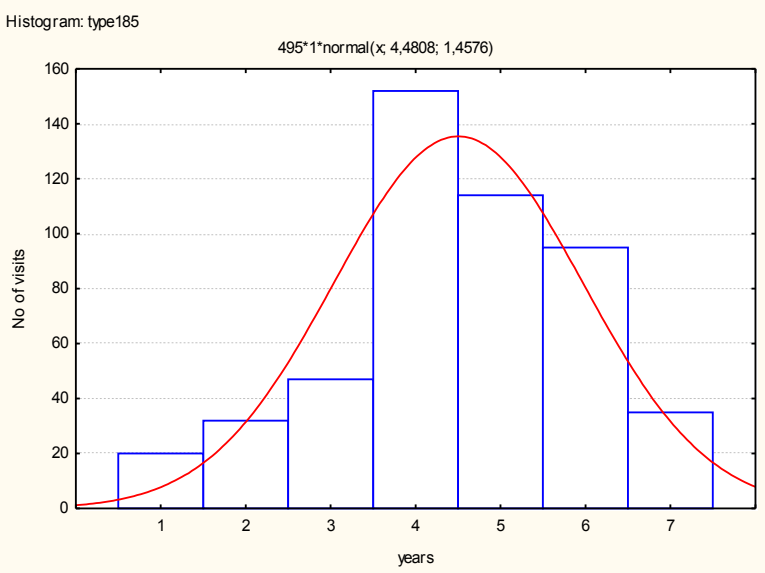
Graph 5.3 There is significant periodicity at both histograms of entries and out days [A.Jarynowski]

We can look at statistical properties of network in time. Let looks at number of all MRSA infections in time and compare it with type 185.



Graph 5.4. There is a difference between shape of histograms (numbers of infections) for type 185 and it look more like epidemic. Because of that we will consider only this specific type. [A.Jarynowski]

Let also look at number of contacts (as a visits in the same health-care units patients with MRSA type 185). We can observe decreasing number of contacts, instead fact, that there are more and more infected. The reason is, that hospitals isolate infected as soon as they find their disease after testing positive. That stops epidemic.



Graph 5.5. Visits MRSA-185 infected in the same unit in time intervals [A.Jarynowski]

5.6b)Simulated data analyze

Then we can look at how MRSA is spreading in time and tried to simulate similar scenarios using MCMC Markov Chain Monte Carlo- class of algorithms, which are based

constructing a Markov chain that has the desired distribution as its equilibrium distribution[25].

•Matrix of transition in time interval. We assume that vector of our population (0-health, 1-ill) evaluate in time.

•We want to find mechanism of change.

0 0 ... 0 1 ... 0

0 1 ... 0 1 ... 0 change after time interval

•All individuals can have specific *p* (probability transition). We can estimate that probabilities using historical data and try to run MCMC to predict future states.

How will it work practically? the main problem are vectors *p*, but we can take them from matrixes P_i and look if method give similar states after averaged simulations and historic data. Firstly we will try that mechanism on simple model and then on historical data. If Yes we can investigate MCMC later to get most likely paths.

How does exactly calculate *p* (transmission probability)? In individual case -if we have state *i*- (vector of our population) we take matrixes P_i and vector P'_i (we do not care about all matrix ill vs patient but we introduce new measure of intensively of contact: person*day)to get state *i* (because we have in that matrixes all information about all patients with their contacts with potential senders and theirs statistical characteristics of theirs individuals characteristics of being potentially infected).

In a first step we try to start with a vector of 291 patient, who have MRSA-185. At beginning only one patient was ill (was tested positive during 1 year). This patient is placed in 141 column of state vector. So first state has 290-zeros and only one-1. Our goal is to get at the end of simulation also similar number of infected. We calculated matrixes *P* and vectors *P'* for each years, but there are not normalized. We need 2 parameters:

•*s*- normalization on influence of contacts with infected (there is important to treat all of possible senders individually to find path of transition)

•*m*- normalization on influence of contacts with infected (there is no need to treat it individually, so the best measure is person*day)

There is also third parameter *n*- as we showed before ¼ of all infections cannot be explain

25 Robert P „Monte Carlo statistical methods" 2002

at all by a social network. We introduce it into a model respectively to time step(partly each year) to get rate of ¼ at the end of simulation.

To get the most likely probabilities let use Metropolis Algorithm. One (tested positive) has more influence on the sending infection, whereas the second one(not tested) is also included pressure. We studied, via computer simulations (like Ising model with Metropolitis Monte Carlo algorithm), the interplay between states in depends on such factors as: fraction of contacted infected, and the possibility of contact between all patient. That model has it roots in the domain of magnetism, but the meaning of magnetic spins has been changed into health states (0-health or ill-0).

We can write it as a quotations in an algorithm with remaining that testing of changing state base on exponential function of quantitative variable parametrized with normalization coefficient and compared with random variable.

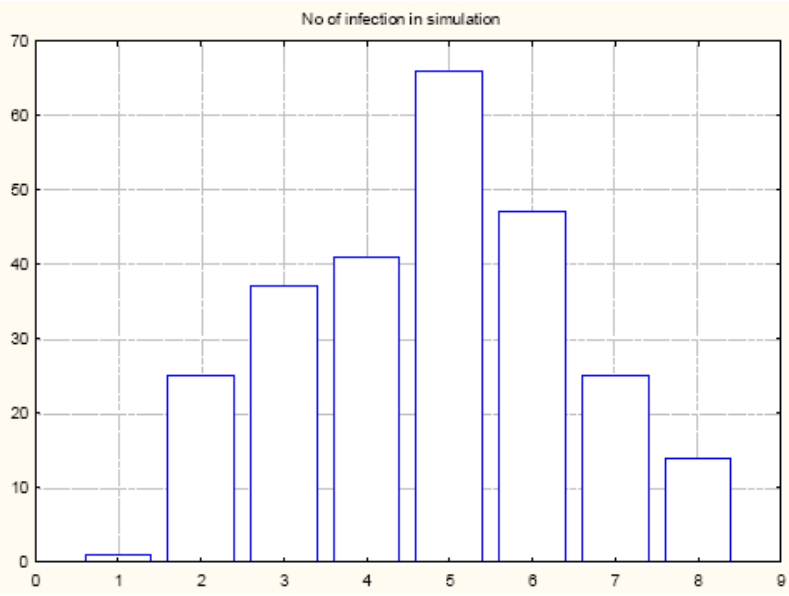
```
For i=1 To 291 ‘
        If State(i)<>1 Then
            For j=1 To 291
                If P.Value(i,j)<>0 Then
                    If Rnd()>Exp(-P(i,j)*s) Then
                        NewState(i)=1
                    End If
                End If
            Next
            If Rnd()>Exp(-P’(i)/m-n) Then
                NewState(i)=1
            End If
        Else
            NewState(i)=1
        End If
Next
```

After some simulation We choose the best parameters (we have started simulation with parameters transmitting mean values to probabilities to 1/3):

- s=10 (we can tune it and change influence of contact with all infected)
- m=800 (we can tune it and change influence of contact with all patients)

	1 Zmn1	2 Zmn2	3 Zmn3	4 Zmn4	5 Zmn5	6 Zmn6	7 Zmn7	8 Zmn8	9 Zmn9
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	1	0	1	0	0	0	0	0	1
4	1	0	1	0	1	1	1	0	1
5	1	0	1	0	1	1	1	1	1
6	1	1	1	0	1	1	1	1	1
7	1	1	1	0	1	1	1	1	1

Picture 5.9. Part of results of simulation (it has originally 291 columns). In rows are states in each steps of simulations (in first row is initial state). In column are individuals. We can observe how system is evaluating in time. At the end we have got a state with almost all ones (that was a criterion of choosing parameters). [A.Jarynowski]



Graph 5.6. Histograms (numbers of infections) for type simulated date. Look at the graph 5.4 (on right) and compare with real situation. [A.Jarynowski]

5.6)Discussion

The research showed that, as expected, infection were more difficult to be explain with this dataset. We can produce simulated states which are based on real in the beginning. The influence of contact with infected turned out to have a larger impact on path transition. We can find in future averaged p-vectors of state transition extended to individual possibilities of sending infections(this is very important to have most likely path transition). Next step is also to run that simulation not only for 291 infected patient,

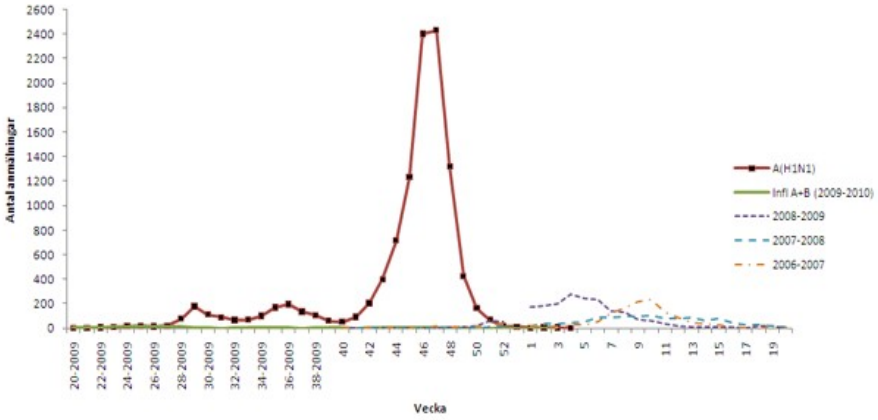
but for 107351 (all patients, who had contact with any infected person).

Another thing which can be done: an artificial networks:

Simulating networks with similar parameters of contacts as real data. Comparing with real data matrix. There could be built simple model of infection spreading (main parameters will be number of contacts with patients and with infected during specified time interval). From that model we will get matrixes P' and P to compare with realistic ones.

Summary

The aim of this work was to show few examples and few perspective of mathematical modeling in epidemiology. We began with differential equations which were a first tool to describe and predict that phenomena. Wroclaw as a cite was very important, because statistics from smallpox epidemic were used by Bernoulli to estimate parameters of first mathematical model of epidemic (chapter 1.2). Next step were SIR models and those also appeared first as differential equations (chapter 2). They were very popular in begin of XX century. When computer simulation changed the world of mathematical modeling agent-based models gave more possibilities in epidemiology. That models (chapter 3 and 5) have a big privilege on differential equation, because of information of social network, people habits and reaction on infections, which can me involved in agent-based models as well as governmental intervention. We showed in this work how that human relation are important in transmitting diseases and there are institutions, whose aim are to decrease cost of epidemic in societies (like ECDC: European Centre for Disease Prevention and Control). In recent years, the knowledge of social networks experienced an accelerating growth. To solve more complex and sophisticated social problems, new types of tools and models are constantly developed. Simulation modelling is very important because it provides the insight into the dynamics of the social process whereas commonly used methods of research not always make it possible. Moreover, such models allow not only to test theory but also they are inspiring and may support constructing new theories in sociology. The most interesting is the possibility to study the dynamics of collective behaviour itself and the relationships among variables of interest.
As a example we presented H1N1 pandemic in winter 2009/2010. This very sophisticated model is first in history, which calculate states of all agents which represent all citizen of Country (Population of Sweden is about 9 millions). We can observe right now how this model is suitable to real situation. This is the best prove of goodness of that model. Let compare graph below with fig 3.9 (pic 9) to validate this model.



Graph Summary.1. Data of influenza cases collected by The Swedish Institute for Infectious Disease Control (SMI)

Results of that model were used by Swedish policy makers. That shows, that mathematical modeling can by useful and gives answer (in this case about vaccination of all population).

This work was not be full if we wouldn't present cellular automata (chapter 4), because they are something between agent-based models and differential equation. The biggest problem with them is topology. Social network are very complicated and there are difficulties in putting that relations. There is a big difference between "Game of life" and SIR-improved models present in that thesis. Very sophisticated method were used to imitate realistic social networks and put into mathematical topology of Cellular automata lattice.
As a most important results we should think is optimal radius of vaccination (graph 4.1). That give information to policy makers: how optimalize amount of money spend to stop epidemic with the most effective solution.

The most important part of this work is model of MRSA spreading in Stockholms hospitals. Unfortunately, the most important question (about most likely transmission paths) couldn't be answered. Even that we can use mechanism from this work to other fields like criminology. Research made in this thesis give new perspective in epidemiology as well as in criminology. Let consider network analyze in both cases (because some special situation like isolation is similar in hospitals and in prisons). We would like to call sociological definition of total institution, which can describe both

areas of research. A total institution[26] is an institution where all parts of life of individuals under the institution are subordinated to and dependent upon the authorities of the organization. Examples: approved homes, boarding schools, concentration camps, colleges, cults, hospitals, prisons, mental institutions, sailing ships, boot camps, monasteries, convents, nursing homes and orphanages. Robert K. Merton after Erving Goffman hint that the public or totalitarian institutions produce the conditions for which the body depending on their social characteristics (institutions and unified totalitarian forced) must adapt. He distinguished 5 types of deviant behaviour : conformism, innovation, ritualism, withdrawal and rebellion[27]. From sociological point total institutions have a lot of properties, but one is the most important for my approach: there are closed. That results smaller number of social contacts, which can be measured. This assumption give us an opportunity to observe spreading diseases, ideas, opinions etc. That project would follow 2 ways, but both come from register-based data from Swedish total institution and first part (epidemiological) is mostly done. To understand similarity of epidemiological and criminological analyze let follow tables below. Left part is only to remind case describe in details (chapter 5) but right is something new: co-offending analyze.

Contact networks and the spread of MRSA in Stockholm hospitals	**Social networks and criminology**

26 defined by Erving Goffman:*("Characteristics of total institutions")*
27 Merton Robert: *"Social Theory and Social Structure"* 1968

MRSA	Criminology
Background The bacterium meticillin resistant Staphylococcus aureus (MRSA) is resistant against more than half of all antibiotics sold in Sweden. In the end of the 1990s, Sweden was hit by MRSA outbreaks in the healthcare sector in the city of Göteborg. A national MRSA spread was avoided thanks to efficient counter measures which were very costly and cumbersome. Since year 2000 there has been one MRSA outbreak in the healthcare sector in Stockholm. It would be very problematic if MRSA was established in Stockholm hospitals; it would imply high costs to cover for increased care needs and also impose an infection risk for the patients. MRSA would also become a big work environment problem, since healthcare personnel has a key role in the spread of disease. MRSA is spread through direct or indirect skin contact between people. ***Contact networks*** It has for instance been shown that it is easier for a disease to become endemic in a population if there is a large variation in the number of social contacts If persons in the population tend to have contacts with persons who have the same number of contacts as themselves, the risk for a outbreak is increased. Sharing contacts with their contacts in a population has a limiting effect on the outbreak on the other hand. For less infectious diseases, where a close contact is needed for a transmission to occur, the individual's position in the contact network is important for the person's risk to get infected. Today, the term network epidemiology has become an established concept within infectious disease epidemiology.	***Background*** Sweden has a low crime rate with rare, but increasing, instances of violent crime. Criminologists investigating correctional institutions to better understand both the causes of crime and the criminal actor. There is a lot of register-based data in that field. 1950 was the year Sweden began recording national crime statistics[28]. In 1950, 195,000 crimes were reported. In 1964, the number was 368,000. Between 1975 and 1990, the number of reported offences rose by 61 percent at a steady rate. In the 90s, the number fluctuated between years, but was generally not increasing. Recent years have seen a slight increase, but the level of crime is no higher than it was in 1990. Immigrants are overrepresented in Sweden's crime statistics. The percentage of the population in prison is also significantly lower than in most other countries. In the late 1990s a new kind of crime drew the attention of media: muggings among youths. This phenomenon bears a strong relationship to the waves of immigrants that arrived in Sweden the 1990s. ***Contact networks*** In Sweden, youth justice has historically been treated primarily as a youth- welfare problem. Youth involved in crime and drug use therefore constitute a substantial group among those teenagers placed in social services care, and for some decades now, Sweden has had a special category of residential institutions, know as special approved homes. This study uses a network analytical approach to examine co-offending[29]. The aim is to test whether a network perspective can provide fresh insight into the character of crime in metropolitan area. Criminologists proposed dataset from special approved homes, because it is available. We would try also to get data from prisons, but they only have date on very high level of neighbourhood.

28 Statistics from the Swedish National Council for Crime Prevention (Brottsförebyggande rådet - Brå).

29 Sarnecki J. Delinquent Networks. Youth Co-offending in Stockholm Cambridge Studies in Criminology ,2001

MRSA	Criminology
The project's aim The aim of the current project is to increase the understanding of how MRSA is transmitted in Swedish hospitals. Methods to analyze the contact network of persons visiting the same care unit will be developed within the project as well as methods to analyze in what way network structure affects the transmission of MRSA. ***Data*** The project will use anonymized data from two linked healthcare registries; (1) the Common Care Registry (CCR) containing information about all in- and outpatient visits within Stockholm County during the period 2000-2006. The other dataset (2) is a registry over diagnosed MRSA cases in Stockholm County during 1999-2005. CCR holds information on care unit and time and date for all entries and discharges within the inpatient care. It also contains information on unit and date for each outpatient visit.	***The project's aim*** The network perspective is today firmly established within sociological, anthropological and economic thought. These theoretical perspectives see the causes of crime as partially or completely associated with individual's ties to different types of social network. •How do delinquent relation, gangs and criminal underworld influence choice of co-offending? •Is it possible to reduce crime evidences, manipulating with social networks in total institutions? •How are ties, social bonds, interactions, differential associations are connected to crimes ***Data*** Data sources employed include the ADAD, KIA(for approved homes) with duration of standing. There is also available data of co-offending from Stockholm's area(more than 22000 suspected of 29000 offences)

Main method of realization

We study matrix of disease transition in hospitals population(it also can be understand as a matrix of influence to crime). This matrix is our first goal. In rows are Infected (suspected of crime) and in Columns people, who could sent infection (who could influence to committing crime). Elements of matrix are probabilities, what Infection was sent by indicated person. Diagonal elements are probabilities of being infected by someone out of hospital, but they are in first approximation zeros.

MCMC (Markov Chain Monte Carlo) analyze is extension of previous method.

Matrixes of transmission in time interval are investigated. We assume that vector of our population (0-health or not recidivist, 1-ill or recidivist) evaluate in time. We want to find mechanism of change.

0		0	...	0	1	...	0	
0		1	...	0	1	...	0	change after time interval

All individuals can have specific p (probability transition) or better p should come from specific distribution (like in mean field theory). We can estimate that probabilities using historical data and try to run MCMC to predict future states.

MRSA	Criminology
Other methods of realization Artificial networks Simulating networks with similar parameters of contacts as real data. Comparing with real data matrix.	***Other methods of realization*** Artificial networks Simulating networks with similar parameters of contacts as real data. Comparing with real data matrix. Standard sociometric methods like clustering, positions in networks, different measure of social distance, spectral analyze etc.

These are the distinguished phases of this future project:

- Review of various community detection in graphs models and implement their characteristic algorithms. (partly done)
- Review of subsets of all data to find distribution of social contacts for different people. (partly done for MRSA)
- Review of criminological datasets from prisons and approved homes and their co-offending in crimes (waiting for access to databases)
- Implement the error functions for two types of tests. (partly done)
- Compute matrix of probabilities sending infections and spreading idea of crime
- Gather the data of different total institutions and data-mining from other sources like media
- Compare simulated data (from different models) with real ones
- Find paths and patterns of sending infections and spreading ideas of crimes

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