Eur J Med Res (2008) 13: 355-365

MATHEMATICAL MODELLING OF EPIDEMIS UNDER SPECIFIC REGARD OF ADENOVIRAL KERATOCONJUNCTIVITIS

A. Bialasiewicz[1], R. Brehler[2], J. Draeger[3], H. Schmitz[4]

[1]Department of Ophthalmology, Sultan Qaboos University, Muscat, Oman,
[2]Institute of contact Studies IFK, Tating, Germany,
[3]Department of Ophthalmology University Hamburg-Eppendorf, Germany,
[4]Department of Virology. Bernhard-Nocht Institute, University of Hamburg, Germany

Abstract
At first ADV is presented as a typical pandemic.

The contagiosity of adenovirus is high because of the viability of the virus on inorganic surfaces in medical offices up to 35 days. Outbreaks and epidemics occur 3-30 days after infection, which is mainly contracted from medical facilities. EKC is considered a notifiable condition in most countries, and outbreaks, suspects and infections must be reported.

Symptoms like „pink eye", foreign body sensations, photophobia, pain, signs such as follicles, hemorrhages and corneal infiltrates, and vision decrease associated with malaise are frequently observed first in one eye, later involving the fellow eye. Unilateral disease has a high rate of misdiagnosis.

Currently no vaccine or virustatic is available, which is effective, cost-efficient and tolerable. Treatment is symptomatic and antiinflammatory. Late scarring may be amenable to phototherapeutic keratectomy.

Infection control measures focus on the disinfection of equipment and hands of staff, the handling of infected patients with gloves, spatial separation of infected individuals resp. cohorting of infected patients, use of unit-dose eye solutions, and the chlorination of pools by approved and registered disinfectants and germicides.

In connection with this it is shown how to handle the dynamics of infections by mathematical models like cellulare automation, systems of differential equations and to visualize periodic effects by Fourier Analysis and to calculate costs by mathematical programming.

Using mathematical analysis the percentage of a population needing vaccination to prevent spreading of pandemic can be calculated

It is shown here that especially the method of cellular automation is a simple way to simulate complex epidemiological situations without completely knowing the mathematical details.

INTRODUCTION

Up to the 20th century, severe infectious diseases killing thousands of people were common all over the world. Highly contagious, bacterial infections like Plague or Cholera, which were an immanent thread to townships during the Middle Ages, are no longer spreading among people, because modern diagnostics and antibiotic therapy can rapidly stop outbreaks. In contrast to bacterial diseases, even today the specific treatment of virus infections still constitutes a major problem. Epidemics with agents like HIV or influenza virus not to mention yellow fever or dengue in the tropics will continue to affect large numbers of people, unless selective antiviral treatments are available. The spread of such infections among susceptible humans is governed by multiple factors. The kinetics of dissemination of an infection is best reflected by the basic reproductive rate R, which depends on the incubation time and on the time required to reach a maximum of infectivity in the host. Among the different viral infections influenza as an airborne disease is spreading among naïve, not immunized people with high velocity. It takes only three days after exposure until an infected subject can in turn infect others in contrast to SARS, where 15 days are required.

To come to reliable conclusions of how a present or future infectious disease may spread among susceptible humans, mathematical models can be developed, which allow to predict the kinetics of the spread of infection and to analyse the effect of interventions such as quarantine or antiviral drugs.

The model of "cellular automats" , which we will present here, constitutes a both simple and comprehensive model of transmission of infectious agents among susceptible persons.

ADENOVIRAL KERATOCONJUNCTIVITIS

Acute epibulbar infections in humans are one of the most frequently diagnosed eye diseases comprising 2.3-10% of all ophthalmological diagnoses with a prevalence of 0.6-3.5 new cases per 1000 patients. Although almost any microbe can elicit an inflammation in the outer eye about 92% of these are thought to be caused by adenovirus-associated epidemic keratoconjunc-tivitis on clinical grounds. In healthy eyes, most of these infections are self-limited and without late sequelae, but in compromised surface conditions vision-threatening sequelae may result [1, 2, 3].

The identification and notification of patients harboring conditions and infections with a high morbidity (e.g. loss of workdays, high DALYs) and with nosocomial relevance is very important for the economy of a country [3, 4, 5].

This overview will focus on the clinical Ophthalmology of adenovirus infections, which plays a key role In this scenario: the ophthalmologist can make a focussed differential diagnosis taking a detailed history (contacts, course), asking for symptoms, and observing signs by biomicroscopy (localization, type and access of the inflammation). A clinical diagnosis can be established by a morphological examination, and complemented by laboratory evidence of the infectious agent to identify the suspected organism [6, 7]. Close cooperation with infection control specialists may prevent potential harm from the healthy population as well as limit costly laboratory work-ups.

Epidemiology

Follicular epidemic kerato-con-junctivitis (EKC): Adenoviruses are the most important and most frequent cause of follicular epidemic kerato-con-junctivitis (classification according to ICD 10: B 30.0: keratoconjunctivitis by adenovirus, B 30.1: conjunctivitis by adenovirus, B 30.1.: pharyngoconjunctival fever by adenovirus). Adenovirus infections are responsible for 92% of all keratoconjunctivitis cases, and appear mostly in late winter, spring and early summer [3, 8].The viruses implicated are adenovirus Ad1-11, 14-17, 19-22, 26, 29 and 37. The most frequent types in Europe are Ad 8>3>7>19/37, in Japan Ad 8>81 >4>19/37>3, and in USA 8, 19, and 37 [8, 9, 10, 11]. Nosocomial infections have been reported to be associated more often with Ad8, while Ad 7,19,37 are more often associated with infections from the environment such as pools [8, 12, 13]. Adenovirus types responsible for nosocomial infections are defined by mole-cu-lar --epi-demiologic methods such as genome and subgenome typing [14]. Virus shift, appearance of new virus types and simultaneous infections by several virus types can circumvent the type-specific acquired immunity in a population and may result in a new symptomatic outbreak [11, 12, 14, 15].

Acute hemorrhagic conjunctivitis can be caused by Ad8 and (rarely) Ad11 in addition to enterovirus 70,71, and coxsackie-virus A24, B_2 [3, 16]. This adenoviral inflammation is also self-limited, however, symptoms disappear after 6 days, faster than the non-hemorrhagic variant.

ARD-associated keratoconjunctitivis: Adenovirus-associated acute respiratory disease (ARD) with conjunctivitis has been first reported in military recruits during World War II. Epidemics of febrile disease with conjunctivitis can be due to waterborne transmission of Ad4 and Ad7 from inadequately chlorinated swimming pools and small lakes [17]. ARD is most often associated with adenovirus types Ad4 and Ad7.

Transmission

Direct inoculation by fingers is to be considered a major mode of transmission when taking into account that the eyelids and tarsal conjunctiva are touched around 14 times per day unvoluntarily, and additionally voluntarily during make-up or application of facial cosmetics. Person-to-person transmission of adenovirus 8 is established to primarily occur through hands of personnel and/or other persons in contact with patients , and outbreaks originating in health units can often be traced down to one or a few health care providers [9, 18, 19, 20].

In nosocomial infections inadequate handwashing by health-care personnel between patient contacts and inadequate disinfection of equipment is the main risk factor for an outbreak or an epidemic. In larger teaching hospitals (>500 beds) the attack rate of patients with EKC has been estimated at 4.7 per 1000 treatment cases. Transmission may also occur as smear droplet infection in crowded health institutions or in overpopulated areas with lacking personal hygiene and behavior and (Ad 8, 19). Me-dical and paramedical staff mainly in ophthalmic units and hospitals are the most frequent sources of infections [6, 13]. In addition, the improper use of dropping bottles and vials with contaminated tips, tonometer tips and other inadequately disinfected contact instruments, inappropriate patching or multiple use of contact lenses are other important risk factors.

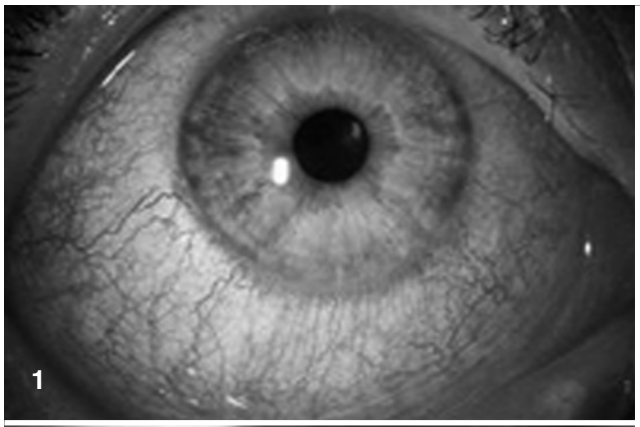
Contagiosity

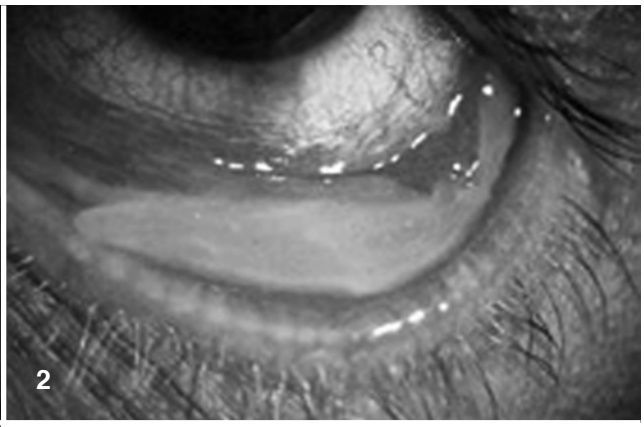
Adenoviruses are exceptionally stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body. Thus the high rate of transmission in an ophthalmic unit, e.g. the contagiosity of adenovirus-associated EKC can be best understood when considering data of Ad19 being viable up to 8 days on paper, 9 days on tonometer tips, 10 days on textiles and metal and up to 35 days on plastics [21]. These results emphasize the need for proper selection and application of germicides for use in disinfecting noncritical surfaces and semicritical medical devices, such as applanation tonometers, in order to prevent outbreaks of epidemic keratoconjunctivitis.The necessity for the implementation of infection control measures also seems to result from these data and lacking effective medical treatment [22].

Clinical Picture – Adults

Symptoms: Patients diseased with the complex of "epidemic keratocon-junctivitis" complain about unilateral (right or left depending on handedness), itching, tearing, burning and foreign body sensation as well as photophobia. In case of AHC, extensive epibulbar and tarsal hemorrhages and precervical lymph node enlargement may manifest as early as 48 hours after the first symptoms in >90% of patients.

Signs: Biomicroscopy reveals a serofibrinous, sometimes mucopurulent exudate accompanied by chemosis, hyperemia and swelling of the plica (Fig. 1). Tarsal and epibulbar follicles (and petechial hemorrhages in case of Ad3,4 (Fig. 2) appear. Corneal sensitivity is not affected. After a few days, multifocal non-vascularized centrally located nummular corneal infiltrates follow in 95% of cases. They consist of dendritic cells, lymphocytes, histiocytes and fibroblasts (Fig. 3) [23]. Rarely, a superficial punctate keratitis may present, particularly with Ad8. An esthesiometry should be done in all cases of corneal signs in order to differen-





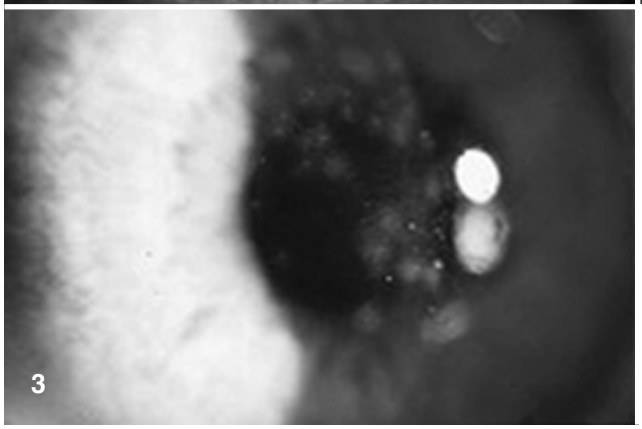


Fig. 1. Epidemic keratoconjunctivitis: 20 year old patient featuring conjunctival hyperemia, chemosis, plica swelling and accompanying reactive tearing

Fig. 2. Epidemic keratoconjunctivitis: 35 year old AIDS patient with severe pain and pseudomembranes on the lower tarsal conjunctiva.

Fig. 3. Epidemic keratoconjunctivitis – sequelae: 46 year old patient 7 days after start of clinical symptoms with persistent pronounced central subepithelial corneal infiltrates with a free zone towards the limbus. Photophobia, visual impairment.

tiate potentially blinding herpetic disease from adenovirus infections. Tarsal pseudomembranes, which consist of necrotic tissue and fibrin on an intact epithelial surface (caveat: no hemorrhage when being removed), can be seen in acute fulminant disease (Fig. 2), and in association with immunodefi-cien-cy syndromes (Fig. 5). They tend to form conjunctival scars and mild symblephara.

Preauricular, submandibular and cervical lymph node swelling are typically associated with all adenovirus infections, and can be seen and palpated in acute hemorrhagic conjunctivitis 48 hours after onset of symptoms. Lid edema, secondary inflammatory ptosis, and an upper respiratory tract infection as well as severe malaise may accompany some cases. ARD is particularly pronounced in Ad3 and Ad4 infections of adults and in Ad7 and Ad8 infections in children.

Sequelae (Fig. 3): The clinical symptoms of EKC and AHC are generally self-limiting after 2-3 weeks resp. 4-6 days, However, even after 2 years nummular corneal lesions and a decrease in vision from 1.0 to 0.5 can be biomicroscopically documented for Ad8 infections in 47% of patients [24]. Adenovirus can be isolated from the conjunctiva of a cohort of patients in a decreasing time pattern - about 50% of patients after 10 days are still infective, some remain infective for more than 2 years. In case of AHC, Ad2, Ad3, Ad4, Ad5, Ad19 can also be isolated even several months after onset.

Any cytopathogenic agents infecting the ocular surface including the adenovirus result in a postinfectious dry eye syndrome due to the loss of goblet cells. This event is clinically relevant in about one third of patients. This may sometimes be difficult to differentiate from an ongoing infection. The differential diagnosis can be made utilizing tests such as Schir-mer's , Bengal rose, break-up time, tear film interference, and impression cytology.

Clinical Picture–Neonates

Neonatal adenovirus infections involving of the eye are rare compared to the frequent bacterial inflammations. Conjunctivitis has been reported in neonates surviving systemic disease [25].

Symptoms: Simultaneously bilateral „red eyes" and tearing can be easily differentiated from the mucopurulent exudate in bacterial infections.

Signs: Lacrimal gland swelling, lid edema, conjunctival hyperemia, and conjunctival papillary reaction can be observed.

Sequelae: The clinical symptoms are self-limited after less than 10 days, and compromising corneal disease and vision impairment has not been reported yet.

Risk factors: It has been documented in Heidelberg recently that the prior examination of neonates by ophthalmologists for screening of retinopathy of prematurity was the only significant risk factor for subsequent adenovirus conjunctivitis in the newborn [13].

Laboratory Diagnosis in Ohpthalmology

In the differential diagnosis of microbial conjunctivitis, particularly in immunocom-promised patients, a laboratory diagnosis supporting and detailing the clinical impression is desirable. Since sometimes multiple types of adenovirus can contribute to an outbreak or epidemic, typing is of considerable epidemiologic relevance. A dacron- or wood-tipped applicator for conjunctival swab should be inserted deep enough (caveat: use topical anesthetics and NaCl moisterization for ap-

plicators) to have epithelial cells scraped. The material can be forwarded in commercially available virus transport media, e.g. VT8 for culture, which is still the reference method, however slow (5-33 days) and troublesome. The more practical method is the quantitative real-time PCR to prove nucleic acid of Ad3, 4, 6, 7, 8, 14, 19, 37, which are particularly important in Europe [6, 7]. Enzyme immunoassays are a cheaper and faster option with a high sensitivity of 91%, however, they bear a variable specificity depending on contaminations and false positive results. Even cheaper are direct immunofluorescence test, which have a very variable sensitivity and specificity and are therefore currently not recommendable for a molecular epidemiologic investigation. For immune dot-blot tests, the sensitivity is 67-84% [26] compared to culture, and for the bedside immuno-chro-matographic test it is 95% [27].

Treatment

Prerequisites: In all self-limiting diseases the evaluation of treatment trials is difficult. Success concerning the disappearance of the infection is often measured by less organisms to be found at the site of infection, less subjective symptoms, amelioration of inflammatory signs (e.g. conjunctival hyperemia, exudate, corneal involvement) and decrease of morbidity (e.g. office presentations).

Medical - curative: Experimental and clinical success has been reported for topical alpha-interferon [28], cidofovir [29], PVP-iodine 5% [30]. However, none of these agents could withstand the test of cost-effectiveness or freedom of limiting side-effects. As well, the most promising substance cidofovir has been doubted to be effective at all in clinical trials [31].

Currently, N-chlorotaurin, which has been proven to be effective against adenovirus and adenovirus infection in vivo and in vitro and has been reported tolerable is entering a phase III clinical trial. However, data regarding the actual shortening of the disease, the duration of symptoms, and the effect on shedding of virus in humans have not yet been reported and are difficult to obtain in a self-limiting disease anyway [32, 33].

The use of antiherpetic medications such as arabinoside [34], iodine-desoxyuridine [35] or trifluorothymidine [36] has not been successful.

Medical - symptomatic: Topical corticosteroids may mitigate the subjective symptoms and may delay or prevent the development of corneal infiltrates. After tapering the corticosteroids, a recurrence rate of 30% has been reported [24]. It has been documented in animal experiments that the adenoviral replication may increase under the influence of corticosteroids [37]. Therefore, the application of corticosteroids may only be legitimate in massive fulminant infections with the intention to prevent symblephara, corneal scarring and permanent vision impairment. A consensus for the use or the dosing intervals for corticosteroids does not exist.

In only one study topical cyclosporin A has been reported beneficial with regard to the removal or disappearance of corneal infiltrates [31].

Medical - prophylactic: Vaccines had been developed for Ad4 and Ad7 infections (ARD associated conjunctivitis), but they were conceived only for preventing ARD among military recruits and had never been relevant for ophthalmologists [17].

Surgical: Late sequelae such as persisting scars, irregular shaping and irregular astigmatism after EKC may result in a compromised image quality or impairment of vision. In these cases a topography- or wavefront-guided phototherapeutic keratectomy may restore vision [38].

Infection Control

General: Although the beneficial effect of infection control measures has recently been controversially discussed, the mainstream consensus is to pay strict attention to good infection-control practices that may be effective for stopping nosocomial outbreaks of adenovirus-associated disease [5, 6].

Disinfecting agents proven to be active in vitro against the virus have been listed in the Environmental Protection Agency [39] and RKI/Berlin lists of disinfectants. However, the in vitro conditions and interaction between test strains and germicides may not simulate in vivo conditions. For example, Ad2 and Ad7, is susceptible to alcohols after 10 minutes of contact time [40], but adenovirus 8 is resistant to the action of 70% isopropyl alcohol [41]. Thus, research results concerning hygiene issues in adenovirus infections have often been confusing for the practicing clinician.

Maintaining adequate levels of chlorination is necessary and effective to prevent swimming pool-associated outbreaks of adenovirus conjunctivitis.

Ophthalmology – medical staff: The main task of medical staff during an outbreak is to strictly adhere to hand disinfection to prevent person-to-person spread of infection using the recommended germicides, and gloves in between the handling of infectious patients or (potentially) contaminated materials. Of the germicides suitable for use as an antiseptic, 70% ethanol achieved a 3-log10 reduction under four of the five test conditions [42].These measures may limit the spread of EKC acutely, and may achieve a long-term reduction of incidence rates [8, 26].

In a convincing comparative 6-year study employing enforced infection control measures in an ophthalmic unit, 0.54 outbreaks involving 5.66 infected patients per 10000 patient examinations have been documented in contrast to 3.89 outbreaks involving 54.09 infected patients per 10000 patient examinations without those measures ($p<0.005$ und $p<0.0005$).

Ophthalmology – equipment etc: Dropping bottles and eye ointment should only be used by one patient, and single-use units should be preferred [43].

Patient-relevant areas, equipment, instruments, and other devices undergoing patient contact like slitlamp accessories must be disinfected with recommended germicides[4], [16], [39].

Tonometry: Contact tonometry with the Schiotz tonometer or the applanation tonometer is a risk factor for EKC, and the pneumotonometer has also has been associated with nosocomial EKC outbreaks [44].

Problems regarding disinfection or sterilization of the tonometers particularly with regard to disassemblement have been elucidated [45]. Tonometers vary in design and material composition; therefore, disinfec-

tion or sterilization procedures that are appropriate for one type of tonometer may not be suitable for another [46, 47]. Adequate disinfection or sterilization cannot be achieved if the instruments are not initially cleaned thoroughly of any organic material that can impede contact between the disinfectant and the microorganism during the disinfection process.

The irradiation of tonometer tips with ultraviolet light (maximal antiviral effectiveness: 253.7nm) has been proven effective in studies using Ad2, but it has not been generally recommended due to the variable dosages in various adenovirus types (ID90 20.0 to 50.0 mWs/cm2) and undefined exposure times [45, 48].

Other contact instruments: Thermal disinfection is preferred at 93°C 5 min in disinfection and cleansing machines, otherwise a virucidal 3% form-al-de---hyde solution may be used for soaking (4 hours recommended contact), or a more practical 5% tosylchloramide sodium solution (10 min. recommended contact) can be applied, for example for three mirror lenses.

Areas: Patient contact areas such as slitlamp accessories must be treated with virucidal preparations or by meticulous cleansing with 70% ethanol for at least 5 min. [5, 39].

Textiles: Contaminated textiles must be treated with a thermal (90°C, 10 min.) or chemo-ther-mal disinfection [40].

Notification

Notification of suspects and/or diagnosed cases of nosocomial adenovirus infections is requested by laws of most Western countries. In Germany the outbreak must be notified according to the Impfschutzgesetz § 6 (3) IfSG anonymously. If laboratory evidence has been found, the notification must be by name according to § 7 (1) IfSG [5]. In the USA, patients must be reported through state health departments to the Epidemiology Branch, Center for Infectious Diseases, Atlanta.

Ways of Mathematical Modelling of Epidemics

Mathematics can apply on the one hand statistics for the description and calculation of epidemics [49] on the other hand especially cellular automations, systems of differential equations, systems of difference equations, Fourier synthesis, linear and non-linear programming.

The model of cellular automation calculates with the concept of an entity consisting of many singularities which obey rules defined only for them [50]. The risk of infection, the course of infectious diseases, including death can be calculated this way. An epidemic can start with only one infected person. The epidemic increases by contact to direct non-immune neighbours with a programmable risk for infection and a programmable rate of hygienic standards. Mechanisms increasing epidemics in countries with different hygienic standards can also be calculated.

In addition to this it is possible to simulate the success of therapy within these programmes. In this way the rate of survivors among recently infected persons can also be determined. These people are immune in the future.

With a given percentage of immune persons the programme is able to include its development simulation of immunity by vaccination. Such calculations show for example, that an epidemic grows not as fast if a certain percentage of the population is vaccinated. In some cases epidemics have stopped after a time, if the vaccination rate was high enough but lower than 100%. In the epidemiology of infections mathematical models calculate with a basis reproduction number R_0. It is the mean number of potential infectious contacts during the infectious period. In case $R_0 < 1$ an epidemic can not spread out [51]. To eliminate an epidemic vaccination is necessary.

Here is an example to demonstrate this more visually: A pandemic spreads from one infected person. Infected persons infect non-immune healthy persons by risk for infection of 80% and a rate of immunity of 5% achieved through vaccination and hygienic and therapy measures of 0%. The infected persons recover and are immune for the future or they die. Fig. 4 shows the progress of the pandemic. The point of intersection of the line of healthy G(t) and dead M(t) people is based on 47 arbitrary units of time. The maximum of infected people I(t) is reached after 53 units of time.

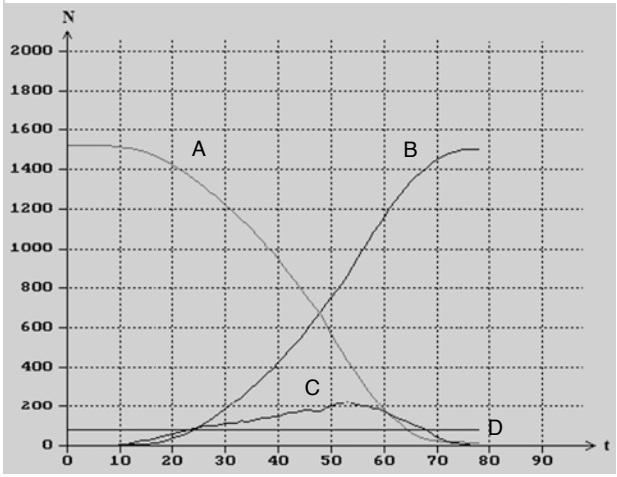


Fig. 4. Progress of pandemic by risk of infection of 80% without hygienic and therapy rates, (A) curve healthy but not immune, (D) curve immune, (C) curve infected but living, (B) curve dead by pandemic.

Hygienic and therapy rates of 60 % and more percent stop the pandemic very fast. Further calculations show that if this is increased to more than 70% there is no spreading of the pandemic anymore. The point of intersection of the line of healthy and dead people on the time axis reaches infinity.

It is clear that vaccination is of use for the unvaccinated people, too for instance by G(t), M(t) and I(t) presented with an hygienic and therapy rate of 60% we can simulate a delay of the spreading of the pandemic and the stop.

It is possible to state the hygienic and therapy variable (HF) with fine structure like this:

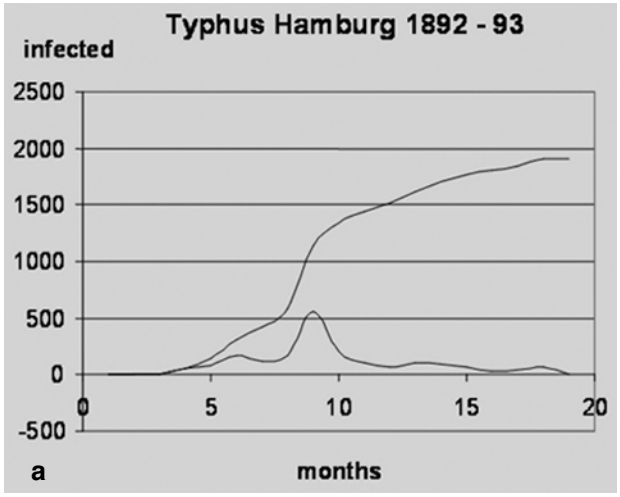
$HF = A \{B_1 + B_2 + B_3\}$.

For instance A can be the quality of drinking-water, B_1 the quantity of water for domestic use like shower

and wash, B_2 cleaning customs and B_3 table customs (eating with chop sticks or cutlery, washing hands before each meal etc.). The influence of the variable A with regard to HF is higher than the influence of the variables Bi. In addition to this you can increase the finer structure by evaluation variables.

Knowing the dependence on time of a pandemic, the hygienic and therapy standards of the past can be estimated. In Fig. 5a and Fig. 5b the increase of typhoid fever [52] and cholera [53] pandemics in the city of Hamburg from 1859 to 1892 are shown. In both cases the upper line states the added number of affected persons. In Hamburg from 1859 to 1892 the variables A, B_1 and B_2 were low. The mortality of typhoid fever was 25% and of cholera 50%. These results can be simulated by the frame conditions for risk of infection 100%, hygiene rate 5%, therapy rate 55% for typhoid fever and risk of infection 100%, hygiene rate 5%, therapy rate 50% for cholera.

The model of cellular automation is limited. Normally we use a two dimensional picture of such an automation like a board of chess with a certain number of squares (cells) and rules for the interaction between the squares. It is usefully to shape this board of chess like a torus and to connect both ends of this torus. This body has a finite inner and outer surface without a border. Calculation of conditions for the near future can be done step by step for each square randomly to the next cell or simultaneously. Apart from normal cells, additional cells can be defined with different rules from normal cells. Influences on neighbouring cells like an infection can only be made to the nearest neighbour around a corner or around an edge of a cell.



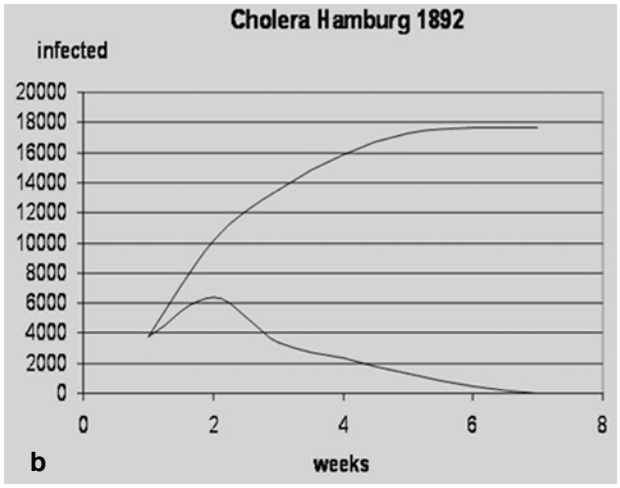


Fig. 5a. Course of typhoid fever epidemic in Hamburg 1892/93 (lower curve), accumulated (upper curve).

Fig. 5b. Course of cholera epidemic in Hamburg 1892 (lower curve), accumulated (upper curve).

A calculation with three types of cells will be shown: Empty spaces, non-immune healthy persons M and people dying by HIV-viruses V. The M- and V-cells move randomly in the area of our board of chess. A change of positions is possible. This is always done with new neighbours. After each step of simulation the simulation continues with a new state of the central cell. If the new central cell is an empty space, nothing will happen, if it is a person, the programme can test, if a neighbouring place is a free one. In this case a new being will be installed (birth), not depending on an increase of its growth rate. If the central cell is an infected person V, the programme will check, if a neighbouring cell is a person or not. If there is a person it will be infected. A new centre of infection will be installed by changing a M-cell into a V-cell. In addition to this the V-cell can turn by a death rate into death. This part of the programme decides, if the new virus cell dies or survives.

The result of this simulation is shown in Fig. 6. This simulation leads to periodic cycles of the number of human beings infected by deadly viruses with displaced phases. Both curves arrive at an average.

The main advantage of this method of cellular automation is that no knowledge of mathematic theories to simulate increasing or decreasing rates regarding time is needed.

Systems of differential equations have derivations of a minimum of one parameter and they are still at the same time valid. Through systems of differential equations it is possible to simulate the same problems as by the method of cellular automation. Some knowledge of mathematics is needed to construct these systems and a lot more knowledge is needed to solve them. Moreover a lot of systems of differential equation have no solution. It is only possible to come to a result by applying numeric methods.

Supposing there was an increase of human beings M of a region, there would be a constant decrease for the HIV virus V and an increase in the HIV virus V proportional to the number of infected persons. This situation can be simulated by two differential equations like

$$M^1(t) = a\,M(t) - b\,M^2(t) - c\,M(t)\,V(t)$$

$$V^1(t) = -\,d\,V(t) + h\,M(t)\,V(t)$$

This simulation leads to periodic cycles with displaced phases like in Fig. 6, too. But the graphs are smoother because here only averages of values are shown and no chance generator was working on details.

Independent by the mechanisms of spreading a pandemic it will cover more people than existing. If

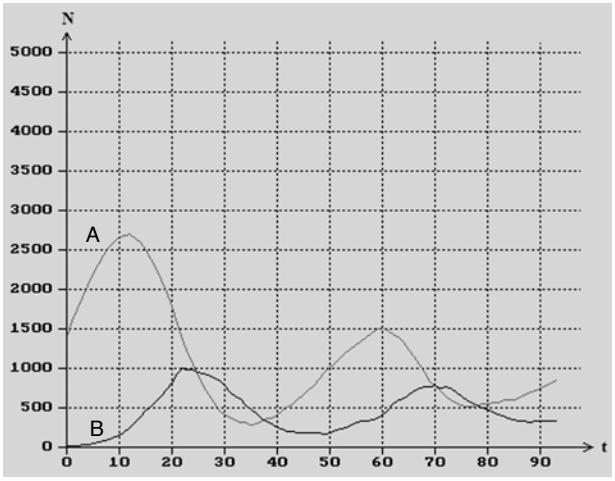


Fig. 6. Simulation of periodic circles human beings (A) curve infected by deadly viruses (B) curve by cellular automation.

G(t) is the number of healthy persons at a certain time, the infection rate dG/dt is proportional to G(t). $dG(t)/d(t) \sim G(t)$. That leads with the parameter σ, to the differential equation $dG(t)/dt = -\sigma G(t)$. The negative sign shows that with increasing time the number of healthy persons decreases. σ is a measure of the aggressive behaviour of the pandemic and respectively for the probability of a change from the status G (healthy) to the status I (infected).

The mathematical solution of this differential equation is $G(t) = G_0 \exp\{-\sigma t\}$, in which G_0 is the number of healthy persons at the beginning of a pandemic.

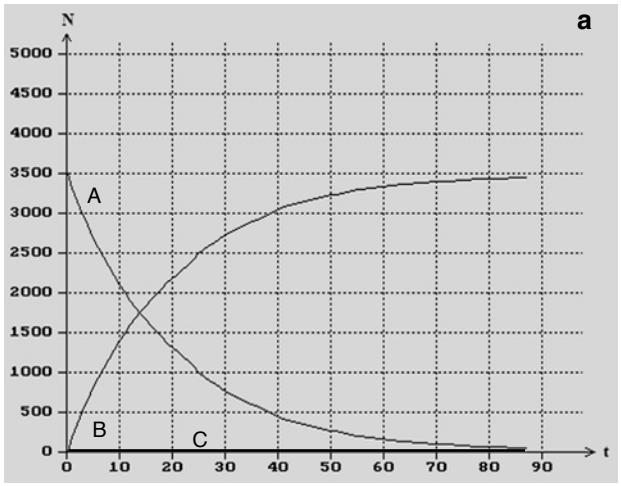
Because the sum of healthy G(t) and infected I(t) persons is always constant, the results shown in Fig. 7a are consequently happening. If you add the curve $I(t) = G_0 (1 - \exp \{ -\sigma t\})$ and $G(t) = \exp \{ -\sigma t\}$ you will find $I(t) + G(t) = G_0$.

A comparison of the curve I(t) in Fig. 7a shows differences with measured values as plotted in Fig. 7b, a schematic draw of 23 registered cases for PLA, ADV, YEN, CLO, HBV, SPA, FSV, COX, MYT, VCA, STY, RTV, CAM, CJK, MSV, GIL, ECO, INV, LEP, LEG, LIS, NEI and NWV [54] during the starting phase. Theory and practicability come together, if we postulate minimum one intermediate stage with pre-infected persons V(t). The transfer from one phase to the other is defined by the transfer probabilities σ and τ: $G(t) > \sigma > V(t) > \tau > I(t)$.

Fourier Synthesis signifies a combination of a curve by sinus and/or cosine with different frequencies. For instance an application in medicine Fig. 8a shows the terraced profile of Proteus Mirabilis on an agar [55]. The situation can be described by the equation $f(x) = b/\pi(-\sin\{2x\} - [\sin\{4x\}]/2 - [\sin\{6x\}]/3) + b/2$.

The first term describes the periodic slow-down of the cell caused by shortage of nutrition. The second term defines the tendency for the formation of normal bacteria. The third term describes the variation of the density of the extended lawn.

The evaluation for ADV from 2001 to 2004 [54] in Fig. 8b shows three typical maxima. The mathematical simulation of this experience is given in Fig. 8c.



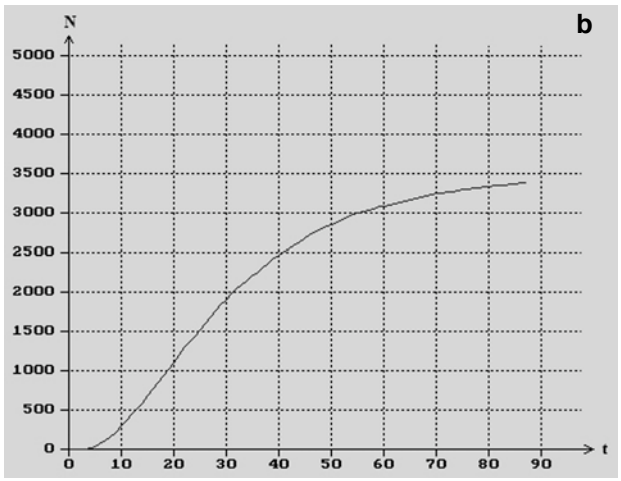


Fig. 7a. Start of pandemic without preinfection, (A) curve healthy but not immune, (B) curve infected persons, (C) curve immune.

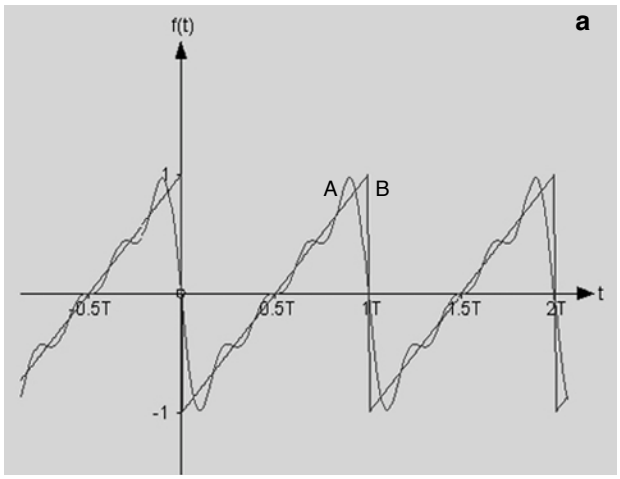
Fig. 7b. Sum of 23 measured cases of pandemics, infected persons versus time.

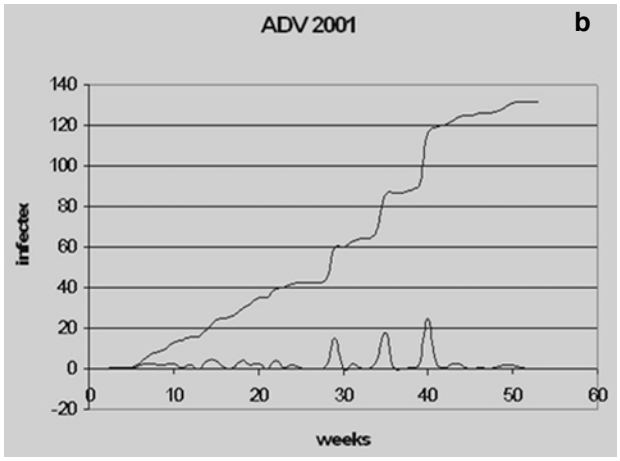
This curve can be analysed by Fourier analysis: $N = 0.4 \sin\{1\omega t\} + 0.66 \cos\{3\omega t\} + 0.5 \cos\{6\omega t\} + 0.23 \cos\{9\omega t\}$.

The interpretation (see Table 1) of the four parts of the Adenovirus pandemic describes the seasonal influence within 16 to 17 weeks, the persistence in lymph nodes and viability on plastics of 5 to 6 weeks, the incubation time in connection with the disease time of nearly three weeks and the self-limitation of

Table 1. Interpretation of terms of Fourier Synthesis of ADV course, $\omega = 2\pi/T$, T = 115.5 days.

N	days	interpretation
$\sin\{1\omega t\}$	115.5	influence of the season
$\cos\{3\omega t\}$	38.5	viability on plastics, persistence in lymph nodes [21]
$\cos\{6\omega t\}$	19.25	incubation time plus disease time [9, 18, 19, 20]
$\cos\{9\omega t\}$	12.75	self limitation of ADV [3, 8]





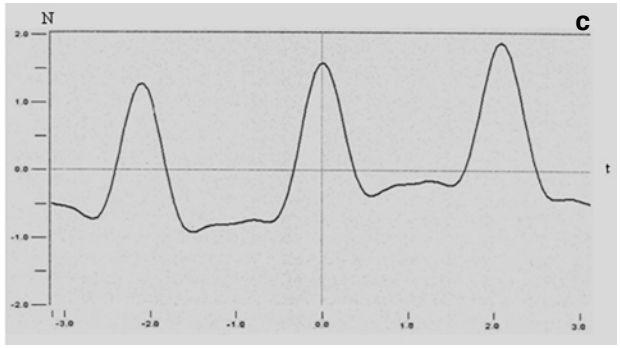


Fig. 8a. Simulation of terraced profile of Proteus Mirabilis on an agar by Fourier Synthesis (A) curve, ideal line (B) curve.

Fig. 8b. Course of ADV in 2001 (lower curve), accumulated (upper curve).

Fig. 8c. Simulation of course of ADV by Fourier Synthesis, N- and t-Axis in arbitrary units.

the pandemic after nearly two weeks, that they are caused by the seasonal appearance of ADV, that most infections come from the consulting hour of oculists and that the rhythm of infection during the consulting itself done by the life time of ADV on the surface of instruments and by the rhythm of infection in the waiting hall of the oculists done by non disinfected door-handles. (see part 1of this paper).

It is easier to get an overview of the epidemiology of plant diseases because of the better chances of experiments. For monocycle diseases the deterministic equation is $K = k (1 + r n)$ and for poly cycle diseases the equation $K = k (1 + r) \exp\{n\}$ with r as the rate of regeneration is well known [58]. Instead of bacteria and viruses funguses dominate germs. They are following a life-cycle and get transfused by chains.

Operations Research gives us the chance to optimize the goods for life and the needs we have.

The aim is to maximize profits or to minimize losses [57, 58]. A differential analysis is in this way helpful to find relative maxima or minima only, if a continual and differentiable function is known [59, 60]. If the question asks for absolute maxima or minima or in case of frame conditions like unequations, we need the help of Operations Research. The simple case is the Linear Programming with linear connections between the parameters. Non-linear Programming is more difficult [61], [62] on the one hand, but on the other hand nearer to reality.

Under the condition that the infection rate I is larger or lower as a hygienic rate H, and if in addition to this all infected persons I will get contaminated K, this is a connection between H, I and K like $H > 1/I = 1/K$.

That means that in Fig. 9 the area above the curve $H = 1/K$ number room we discuss about hygiene and illnesses. Ill people K causes costs a K and provision for hygiene H causes costs b H, too. With the help of the equation $Z = a K + b H \rightarrow \min.$ we describe the minimization of total cost. This equation leads to the linear curve $H = - a K/ b + Z / b$ in Fig. 9 and gives us the point of minimum cost were $H = 1/K$ has the same gradient. In addition to this graphic solution we can come to an arithmetical solution by derivation of the equation $H = 1/K$ that is $dH/dK = -1/K^2 = -a/b$. The solution is $K = SQR \{b/a\}$ and $H = SQR \{a/b\}$.

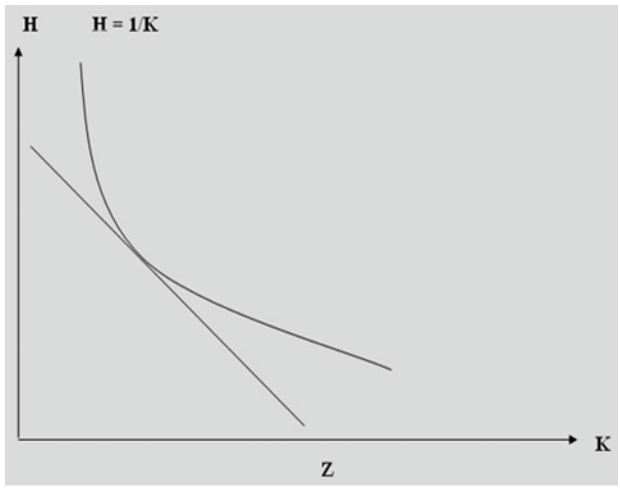


Fig. 9. Range $H > 1/K$ and objective function $H = -K a/b + Z/b$.

Table 2 shows the minimal cost for different frame condition in the variables H and K. As the last column shows, a minimum of cost is realized, if H = K. For

Table 2. Costs for different frame conditions in the variables H and K.

Cost function	H	K	Z
Z = 4 K + 2 H	1.41	0.70	5.62
Z = 3 K + 2 H	1.22	0.82	4.89
Z = 2 K + 2 H	1.00	1.00	4.00
Z = 2 K + 3 H	0.82	1.22	4.89
Z = 2K + 4 H	0.70	1.41	5.62

the practical appliance of this knowledge of health care for the infected people and for hygienic conditions vaccination costs etc. are needed.

The risk of mortality by ADV is < 2%. The costs of disease are twice as much the costs of hygiene. Table 2 shows that on this condition the minimum of costs is 5,62 units. To come to the absolute minimum of costs of 4,00 units the costs of disease must be decreased by increase the hygiene (RKI guideline or intern planes of hygiene).

There is the danger that we can have not enough stockpiling of vaccine in case of HPAI (high pathogen avian influenca). Such analysis of stockpiling of vaccine can be discussed by means of rules of growth [51].

Prognoses of the consumption of medicine like vaccination during a pandemic or the size of stock are extrapolations from the past to the future. Details can be estimated with the help of laws of growth.

You can distinguish between linear, exponential, cumulative, stringed and logistic growth. If the percentage or the absolute number N(t) of an infected population increases we call it linear growth. Included is the trivial case $N(t) = N_0 = \text{const}$.

If in equidistant time steps the increasing rate doubles itself, we call it exponential growth.

The sum of the timely growth is called cumulative growth. The time gap until the cumulative consumption of vaccination is used up is the range R of the vaccine stock.

$$W(t) = \mu N_0 \, dt = W_0 + r_1 t$$

It shows that during constant monthly (or yearly) use cumulative consumption increases linear with time. W_0 is the cumulative consumption at $t = 0$ and r_1 is the linear growth rate. The static range of the stock TS is determined by the ratio of stock and monthly (yearly) consumption: $TS = N/N_0$. We get the following rate for a monthly (yearly) percentage by increasing of monthly (yearly) consumption: $dN = r\,N(t)\,dt$, where r is the increasing rate of increase.

Integration of this differential equation leads to the law of the exponential monthly (yearly) consumption $N(t) = N_0 \exp\{r\,t\}$, where N_0 is the consumption at the time $t = 0$.

You find the cumulative growth of the vaccine consumption from $N(t) = N_0 \exp\{r\,t\}$ by Integration:

$$W(t) = \mu N_0 \exp\{r\,t\}\,dt + c = W_0 \exp\{r\,t\},$$

W_0 is the cumulative consumption of vaccine until $t = 0$.

Problems with the exponential growth will be caused, if the exponentially growing parameter is limited.

You can study influences of growth rates, start of consumption, stock and kind of growth of the range.

The reason for the high growth rates of medicine against HIV in underdeveloped countries is the stringed growth of the population B(t) and the need for medicine per person. If K(t) is the monthly (yearly) consumption of medicine per person and N(t) the monthly (yearly) consumption, we get the function:

$$K(t) = N(t)/B(t) \quad \text{or} \quad N(t) = B(t)\,K(t)$$

With the presupposition $B(t) = N_0 \exp\{b\,t\}$ and $K(t) = K_0 \exp\{k\,t\}$ this results in the monthly (yearly) consumption

$$N(t) = B_0\,K_0 \exp\{[b + k]\,t\} = N_0 \exp\{r\,t\}$$

In this case the increasing rate of the population and the growth rate of the consumption per person were added.

The model of a logistic growth starts with the estimate of the exponential growth with a modified W by the factor $(1 - W/Wg)$. It follows that $dW = r\,W\,(1 - W/Wg)$ with $Wg = W_0 + R$. The solution of the differential equation $dW = r\,W\,(1 - W/Wg)$ is:

$$W(t) = \frac{W_0 \exp\{r\,t\}}{1 + W_0/Wg\,(\exp\{r\,t\} - 1)}$$

and leads to the monthly (yearly) consumption $N(t) = dW/dt = r\,W\,(1 - W/Wg)$.

The laps of the growth rate can be calculated by the ratio of the first derivation of the monthly (yearly) consumption and the monthly (yearly) consumption itself:

$$r(t) = [dN(t)/dt]\,[1/N(t)]$$

The amount of the first derivation of the growth rate is a measure for the so called crisis factor $KF(t) = |\,dr(t)/dt\,|$.

Prognoses for the consumption of medicine like vaccination during pandemics and for the stock are extrapolations of the past into the future.

Medicals must more calculate, to control pandemics, but it is not necessary to learn how to set systems of differential equations and to solve them.

As shown before the method of cellulare automation is equivalent and easy to handle. It is a good tool to calculate and to describe the development of pandemics versus time.

In addition to this the Fourier Analysis allows to check up the fine structure of pandemics.

The costs of vaccination and of other medicine are important for a fight against pandemics. Non Linear Optimization is a way to minimize the types of costs come together.

Some work is done, more is to do.

REFERENCES

1. Krumpaszky HG, Klauss V (1996) Epidemiology of blindness and eye diseases. Ophthalmologica 210:1-84
2. Bialasiewicz AA (2000) Nosocomial keratitis. Hyg Med 11:458-463
3. Klauss V, Schaller UC, Bialasiewicz AA (2002) Importance and epidemiology of infectious eye diseases. In: Kramer A, Behrens-Baumann W (eds.): Antiseptic prophylaxis and therapy in ocular infections. Dev Ophthalmol 33:145-190
4. RKI-Ratgeber Infektionskrankheiten – Merkblätter für Ärzte (2004) Keratoconjunctivitis epidemica und andere Konjunktivitiden durch Adenoviren.
5. Bales S, Baumann HG, Schnitzler N (2003) Infektionsschutzgesetz: Kommentar und Vorschriftensammlung. 2. Auflage. Kohlhammer Verlag, Stuttgart, Berlin
6. Cheung D, Bremner J, Chan JT (2003) Epidemic keratoconjunctivitis--do outbreaks have to be epidemic? Eye 17(3):356-363
7. Wolfel R, Pfeffer M, Essbauer S, Nerkelun S, Dobler G (2006) Evaluation of sampling technique and transport media for the diagnostics of adenoviral eye infections / Adenovirus sampling and transport. Graefes Arch Clin Exp Ophthalmol. 2006 Mar 21; [Epub ahead of print]
8. Aoki A, Isobe K, Ohno S (1994) Nationwide surveillance program of epidemic conjunctivitis in Japan. In: Bialasiewicz AA, Schaal KP: Infectious diseases of the eye. pp 309-316, Butterworth-Heinemann, Philadelphia
9. D'Angelo LJ, Hierholzer JC, Holman RC, Smith JD (1981) Epidemic keratoconjunctivitis caused by adenovirus type 8: epidemiologic and laboratory aspects of a large outbreak. Am J Epidemiol 1981;113:44-449.
10. Bialasiewicz AA, Jahn GJ (1994) Augenbefunde bei Virusinfektionen. Dtsch Ärzteblatt 91B:685-694
11. Chang CH, Lin KH, Sheu MM, Huang WL, Wang HZ, Chen CW (2003) The change of etiological agents and clinical signs of epidemic viral conjunctivitis over an 18-year period in southern Taiwan. Graefes Arch Clin Exp Ophthalmol 241:554-60
12. Takeuchi S, Itoh N, Uchio E, Tanaka K, Kitamura N, Kanai H, Isobe K, Aoki K, Ohno S (1999) vAdenovirus strains of subgenus D associated with nosocomial infection as new etiological agents of epidemic keratoconjunctivitis. J Clin Microbiol 37:3392-3394
13. Chaberny IE, Schnitzler P, Geiss HK, Wendt C (2003) An outbreak of epidemic keratoconjunctivtis in a pediatric unit due to adenovirus type 8. Infect Control Hosp Epidemiol 24:514-519
14. Kemp MC, Hierholzer JC, Cabradilla CP, Obijeski JF (1983) The changing etiology of epidemic keratoconjunctivitis: antigenic and restriction nzyme analyses of adenovirus types 19 and 37 isolated over a 10 year period. J Infect Dis 148:24-33
15. Majeed A, Naeem Z, Khan DA, Ayaz A (2005) Epidemic adenoviral conjunctivitis report of an outbreak in a military garrison and recommendations for its management and prevention. J Pak Med Assoc 55:273-275
16. Bialasiewicz AA (1995) Infektionskrankheiten des Auges. G Fischer Verlag ISBN 3-437-11517-0
17. CDC (2006) Respiratory and Enteric Viruses Branch: Adenovirus. National Center for Infectious Diseases URL
18. Ford E, Nelson KE, Warren D (1987) Epidemiology of epidemic keratoconjunctivitis. Epidemiol Rev 9:244-261
19. Garner JS, Simmons BP. Guideline for isolation precautions in hospitals. Atlanta: US Department of Health and Human Services, Public Health Service, CDC, 1985; DHHS publication no. 83-8314
20. Reilly S, Dhillon BJ, Nkanza KM (1986) Adenovirus type 8 keratoconjunctivitis--an outbreak and its treatment with topical human fibroblast interferon. J Hygiene 96:557-575
21. Gordon YJ, Romanowski EG, Araullo-Cruz T (1994) Topical HPMPC inhibits adenovirus type 5 in the New Zealand rabbit ocular replication model. Invest Ophthalmol Vis Sci 35:4135-4143
22. Bialasiewicz AA, Richard G (1997) Nosokomiale Infektionen am Auge und krankenhaushygienische Massnahmen in der Augenheilkunde. In: Beck EG, Eikmann T, Tilkes F (Hrsg.): Hygiene in Krankenhaus und Praxis. Bd. 8, III/3.19: S.1-16, Ecomed Verlag, Landshut, ISBN 3 609-76570-4
23. Knappe S, Stave J, Guthoff RF (2005) Epidemic keratoconjunctivitis. In vivo images of corneal structures with the confocal Rostocker laser scanning microscope (RLSM). Ophthalmologe 102(8):798-801
24. Freyler H, Sehorst W (1976) The fate of corneal infiltrations in cases of epidemic keratoconjunctvitis. Wien Klin Wochenschr 28;88:341-343
25. Elnifro EM, Cooper RJ, Dady I, Hany S, Mughal ZM, Klapper PE (2005) Three nonfatal cases of neonatal adenovirus infection. J Clin Microbiol 43:5814-5815
26. Ankers HE Klapper PE, Cleator GM, Bailey AS, Tulo AB (1993) The role of a rapid diagnostic test (adenovirus immune dot-blot) in the control of an outbreak of adenovirus type 8 keratoconjunctivitis. Eye 7:15-17
27. Fujimoto T, Okafuji T, Okafuji T, Ito M, Nukuzuma S, Chikahira M, Nishio O (2004) Evaluation of a bedside immunochromatographic test for detection of adenovirus in respiratory samples, by comparison to virus isolation and real-time PCR. J Clin Microbiol 42:5489-5492
28. Sundmacher R, Wigand R, Cantell K (1982) The value of exogenous interferon in adenovirus keratoconjunctivitis. Graefes Arch Clin Exp Ophthalmol 218:139-145
29. Gordon YJ, Gordon RY, Romanowski E, Araullo-Cruz TP (1993) Prolonged recovery of desiccated adenoviral serotypes 5, 8, 19 from plastic and metal surfaces in vitro Ophthalmology 100:1835-1839
30. Abel R, Abel AD (1998) Use of PVP iodine in the treatment of presumptive adenoviral conjunctivitis. Ann Ophthalmol Glaucom 30:341-343
31. Hillenkamp J, Reinhard T, Ross RS, Bohringer D, Cartsburg O, Roggendorf M, DeClerq E, Godehardt E, Sundmacher R (2001) Topical treatment of adenoviral keratoconjunctivitis with 0.2% cidofovir and 1% cyclosporine: a controlled clinical pilot study. Arch Ophthalmol 119: 1487-1491
32. Nagel M, Teuchner B, Pottinger E, Ulmer H, Gottardi W (2000) Tolerance of N-chlorotaurine, a new antimicrobial agent, in infectious conjunctivitis – a phase II pilot study. Ophthalmologica 214:111-114
33. Teuchner B, Nagl M, Schidlbauer A, Ishiko H, Dragosits E, Ulmer H, Aoki K, Ohno S, Mizuki N, Gottardi W, Larcher C (2005) Tolerability and efficacy of N-chlorotaurine in epidemic keratoconjunctivitis--a double-blind, randomized, phase-2 clinical trial. J Ocul Pharmacol Ther 21:157-165
34. Dudgeon J (1969) Treatment of adenovirus infection of the eye with 5-iodo2'-deoxyuridine. Br J Ophthalmol 53:530-533
35. Hecht SD, Hanna L, Sery TW, Jawetz E (1965) Treatment of epidemic keratoconjunctivitis with idouxirine. Arch Ophthalmol 73:49-64
36. Ward JB, Siojo LG, Waller SG (1993) A prospective masked clinical trial of trifluridine, dexamethasone and artificial tears in the treatment of epidemic keratoconjunctivitis. Cornea 12:216-221
37. Romanowski EG, Zates KA, Gordon YJ (2002) Topical corticosteroids of limited potency promote adenovirus replication in the Ad5/NZW rabbit ocular model. Cornea 21:289-291

38. Quentin CD, Tondrow M, Vogel M (1999) Phototherapeutische Keratektomie nach Keratokonjunktivitis Epidemica. Ophthalmologe 96:92-96
39. EPA (2006) Antimicrobial Pesticide Products. URL www.epa.gov
40. Klein M, Deforest A (1983) Principles of viral inactivation. In: SM Block, ed. Disinfection, sterilization and preservation. Philadelphia: Lea and Febiger, pp 422-434
41. Nagington J, Stehall GM, Whipp P (1983) Tonometer disinfection and viruses. Br J Ophthalmol 67:674-676
42. Rutala WA, Peacock JE, Gergen MF, Sobsey MD, Weber DJ (2006) Efficacy of hospital germicides against adenovirus 8, a common cause of epidemic keratoconjunctivitis in health care facilities. Antimicrob Agents Chemother 50:1419-1424
43. Draeger J, Prueter JW (1990) Importance of diagnosis and preoperative care of the conjunctiva. Klin Mbl Augenheilkd 197:210-213
44. Warren D, Nelson KE, Farrar JA (1989) A large outbreak of epidemic keratoconjunctivitis: problems in controlling nosocomial spread. J Infect Dis 160:938-943
45. Draeger J, Hinzpeter T, Mai K (1969) Tonometer sterilization. Doc Ophthalmol 26:648-663
46. Wood RM (1962) Prevention of infection during tonometry. Arch Ophthalmol 68:202-218
47. Corboy JM, Goucher CR, Parnes CA (1971) Mechanical sterilization of the applanation tonometer. Pt 2. Viral study. Am J Ophthalmol 71:891-893
48. Schmitz H, Draeger J, Emmerich P (1990) Tonometer sterilization. The inactivation of HSV 1 and Ad 2 by ultraviolet irradiation. Klin Mbl Augenheilkd 196:225-227
49. Wassertheil-Smoller, S., Biostatistics and epidemiology: a primer for health professionals, New York, 1995
50. Nüchel, A. Chaosbox , Stuttgart, 1995, p 47
51. Eichner, M., Kretschmar, M., Mathematische Modelle in der Infektionsepidemiologie, Heidelberg (2003)
52. Wolter, F., Das Auftreten der Cholera in Hamburg in demZeitraum von 1831 – 1893 mit besonderer Berücksichtigung der Epidemie des Jahres 1892 – Ein Beitrag zur Epidemiologie der Cholera, München 1898
53. Harterts, H., Geschichte der Hamburger Choleraepidemie von 1892, Hamburg 1892
54. Robert Koch Institut, Berlin, Surv Stat@RKI, 14 April Version 1.05.04
55. Brehler, R., Stübner, G., Beitrag zur Analyse des Schwärmvorgangs bei Proteus Mirabilis, Zbl. Bakt. Hyg., I. Abt. Orig. A 238, 1977, p 383
56. Kranz, J., Epidemiolohie der Pflanzenkrankheiten, Stuttgart 1996
57. Dürr, W., Kleinbohm, K., Operations Research, München, Wien 1992
58. Runzheimer, B., Operations Research I, Wiesbaden 1995
59. Brehler, R., Planungstechniken, Wiesbaden 1998, p 32
60. Brehler, R., Henrich, M., Das Bauprinzip der T. muscularis propria des menschlichen Dünndarms als Grundlage für ein biomechanisches Mobilitätsmodell. Res. Exp. Med. 176, 1980, p. 235
61. Künzi, H. P., Krelle, W., Nichtlineare Programmierung, Berlin 1962
62. Schittkowski, K., More Tset Examples for Nonlinear Programming Codes, Berlin, Heidelberg, London, New York, Paris, Tokyo 1987

Received: August 28, 2007 / Accepted: March 27, 2008

Address for correspondence:
Prof. Dr. Jörg Draeger
Universitätsklinikum Hamburg-Eppendorf
Klinik und Poliklinik für Augenheilkunde
Martinistraße 52
20246 Hamburg
Germany
Telefon: +49-(0)40-46 57 22
Telefax: +49-(0)40-46 85 87 42
E-mail: Prof.Dr.ReinerBrehler@t-online.de