Artigo Original

Development and Evaluation of an on-line Alert System for Meningococcal Meningitis Surveillance

Desenvolvimento e Avaliação de um Sistema de Alerta on-line para Meningite Meningocócica

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ABSTRACT

Objective: To develop and evaluate an epidemic alert system based on real-time electronic notification, running a pilot study for meningococcal meningitis from notification database of São Paulo State. **Methods:** The system was developed in four stages: Inception, Analysis, Construction and Test/Simulation. The Inception covered the requirements elicitation, which defined "what" the system should do. The Analysis involved the modeling and specification rules that defined "how" the system should work. The Construction covered the transformation of defined and modeled rules in programming language. The last stage, Test/Simulation, checked the system under known scenarios, comparing the timing of outputs with the Brazilian notification surveillance framework. In order to make identification easier, the system was named with the acronym VISAO - Vigilance by Information System and Alerting On-line. **Results:** many artifacts were made and some evidences were verified. Some examples of artifacts are the requirements, use cases, class diagram, physical data model, test cases, and algorithms. About the evidences we can mention the fast alert production in simulations of this system as compared with the current procedure in use by health authorities. **Conclusion:** In simulations we observed that in two opportunities VISAO managed to put in evidence outbreak occurrence in advance to the traditional used method by Epidemiological Surveillance Center of São Paulo. In comparison with similar systems under operation, VISAO is distinguished from them in issuing real-time outbreak alerts.

RESUMO

Objetivos: Desenvolver e avaliar um sistema para emissãode alertas em tempo real, baseado em notificações de meningite meningocócicaprovenientes de uma base de dados de notificações do estado de São Paulo. **Métodos:** esse sistema foi desenvolvido em quatro etapas: Concepção, Análise, Construção e Teste/Simulações. A Concepção contemplou a elicitação de requisitos,a qual definiu "o que" o sistema deve fazer. A Análise se preocupou com a modelagem e especificação das regras que definem "como" o sistema deve trabalhar. A Construção abrangeu a transformação das regras definidas e modeladas emlinguagem de programação. A última etapa, Teste/Simul ação, foi responsável por avaliar o sistema a partir de cenários epidemiológicos conhecidos, comparando o seu tempo de resposta com os padrões brasileiros de vigilância em vigência. Para efeito de fácil identificação, o sistema foi batizado com a sigla VISAO – Vigilância Informatizada por Sistema de Alerta On-line. **Resultados:** vários artefatos foram criados e algumas constatações foram verificadas nesta etapa. Sobre os artefatos podemos citar os requisitos, casos de uso, diagrama de classes, modelo físico de dados, casos de teste e programas. Sobre as constatações podemos citar o rápido disparo de alertas nas simulações realizadas pelo sistema quando comparados com os procedimentos atualmente em uso pelas autoridades da saúde. **Conclusão:** Nas simulações, observamos que em duas oportunidades ele conseguiu evidenciar ocorrência de surto antecipadamente ao método tradicional utilizado pelo Centro de Vigilância Epidemiológico de São Paulo. Comparando-o com sistemas semelhantes em p rodução, verificamos que esse sistema se diferencia ao emitir ativamente alertas de surtos em tempo real.

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INTRODUCTION

In May 2005, with the opening of the European Centre for Disease Prevention and Control, the European Union decided to reinforce the use of Early Warning and Response Systems (EWARS)[1]. According to this action, the World Health Organization (WHO) published a report named The World Health Report 2007- A Safer Future – Global Public Health Security in the 21st Century[2], describing the perspective of infectious diseases control by applying information technology.

Brazilian health authority has been investing relevant efforts to fight infectious diseases. Polio and measles elimination are good examples[3]. Nevertheless, many infections are still difficult to control, and among them it is worth mentioning meningitis, flu and dengue.

Meningitis presents high lethality and easy transmission. It had already caused losses to the country in epidemics which happened during the 20th century[4]. Among them, the one which has caused more deaths occurred in from 1970 to 1977. Though the highest incidence was in the year of 1974, reaching almost 180 cases per 100 thousand inhabitants, mortality was higher in 1975 with 411 deaths.

Nowadays, incidence in Brazil is around 3.32 per 100 thousand inhabitants, and in São Paulo State it reaches 4.62[5], making it critical in terms of surveillance and controlling.

In respect to the information technology, Brazilian data systems under operation are[6]: (a) Primary Care Information System (SIAB); (b) Notification Grievance Information System (SINAN); (c) Information System of Newborns (SINASC); (d) Products Information System (SIP); e (e) Mortality Information System (SIM).

The system that owns a close relation with notification of infectious diseases is SINAN that works mainly based on notification and investigation of disease events contained in the list of compulsory notification[7]. Besides allowing the dynamic diagnostic of a case in the population, it registers the characteristics of notified cases and indicates contacts at risk, thus contributing for the epidemiology of a given geographical area.

The process of notification is manual starting with a Notification Single Filling Card (FIN) which is sent to the Municipal Health Authority (MHA) that types weekly FINs into magnetic media sending files to the State Epidemiological Surveillance Center (CVE). The communication between MHA and CVE occurs every 15 days, according to a chronogram previously defined by both. Although SINAN has been built according to previously established specifications and is fundamental for the epidemiological control, the amount of hierarchical levels involved in its structure, the time spent for communication between these levels and manual procedures to operate the system make it slower than expected for the context of epidemiological control. Besides it does not offer immediate and active communication of outbreak and epidemics.

This work describes an information system whose main objective is to issue outbreak and epidemic alert in real time from notification cases at the place of attendance or diagnostic of meningococcal meningitis suspect cases.

METHODS

The system was developed in four sequential stages: (a) Inception; (b) Analysis; (c) Construction; and (d) Tests and Simulation, and will be called from now onwards by the acronym VISAO – Vigilance by Information System and Alerting On-line.

Inception
The stage of Inception has completed two distinguished activities: eliciting requirements and elaboration of use case diagram.

Eliciting Requirements: this activity put in evidence "what" VISAO should do in terms of functional, non-functional and organizational characteristics[8]. With this purpose, there were many meetings with the researchers from Epidemiological Surveillance Center of São Paulo (CVE – SP) along the years of 2006 and 2007, which permitted to understand the current framework of case notification of the Epidemiological Surveillance Centre of the State of São Paulo.

Elaboration of Use Case Diagram: second activity of Inception, the diagram of use case permitted to identify who are the users that would interact with VISAO and what are the main functionalities it should fulfill. To elaborate this diagram it was utilized UML – Unified Modeling Language[9]. Users of VISAO were specified as follow:

System Administrator: responsible for maintaining the basic tables of the system;

Notifier: responsible for notification of cases located in office, hospital, etc;

Receiver: responsible for receiving alerts and make control actions;

Timer: a systemic proceeding, triggered to perform a defined action;

Inference Engine: main module which analyzes notifications and issues alerts.

Analysis
The Analysis stage targeted to transform the requirements obtained in the previous stage in adequate artifacts to the programming language. Three basic activities were completed: specification of use cases, elaboration of class diagram, and elaboration of data model.

Specification of Use Case: this activity permitted

describing "how" VISAO must work. The functioning rules were specified, as well as the requirements and restrictions concerning to system modules. Afterwards they were disposed in a sequential format of logic steps, united by affinity (use cases). Figure 1 presents the sequence of the alert engine main functionality steps, which is the treatment of a new notification.
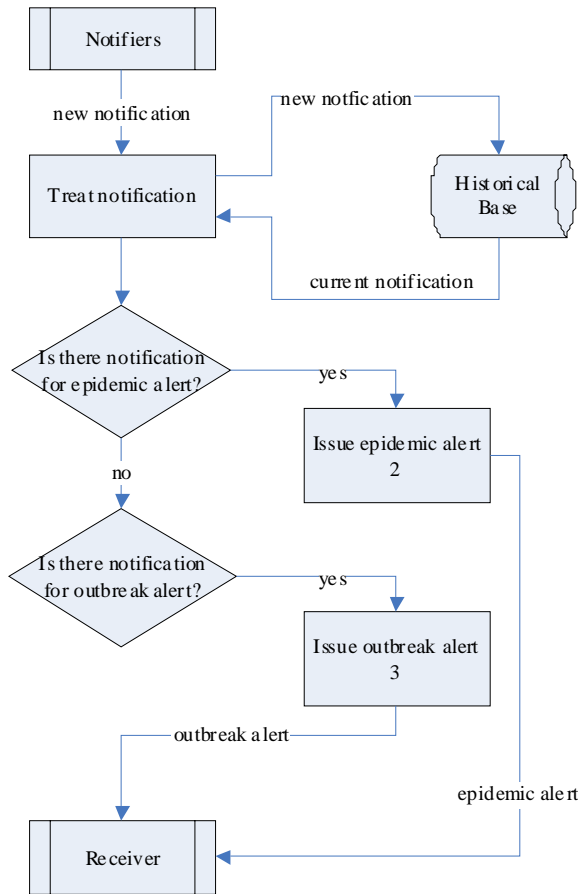

Figure 1 – New Notification Treatment Flow

By receiving a new notification of the suspected disease, issued by notifiers (health office, hospitals, ambulatory, etc.), VISAO searches into its historical base (step 1), notification that contains the same disease reference in the new notification, that belongs to the city and that are still under validity period (incubation period and transmissibility period not overdue). Adding up the new notification to the ones recovered from the historical bases, the system verifies if the number of notification is sufficient for the issuing of an epidemic alert, comparing this number with a parameter pre registered. If this number is sufficient, VISAO issues an epidemic alert (step 2). If this number is not sufficient, the system verifies if the total number of notification is enough to issue an outbreak alert. If it is sufficient, the issuing of an outbreak alert is triggered (step 3).

Both outbreak and epidemic alerts are directed to the responsible staff by the epidemiological control, registered in system. Chart 1 describes the information contained in outbreak and epidemic alerts, respectively.

Elaboration of Class Diagram: this activity controls information that composes VISAO. During the meeting with researchers from CVE – SP documents were rescued (such as filing cards, reports, data sheets, etc.), used to organize and control infectious disease notification, in special, meningococcal meningitis, chosen to be modeled in this first pilot study of VISAO. From those documents relevant information was extracted, necessary for the functioning of VISAO and grouped by affinity through the class diagram, artifact from UML which permitted to have a logical vision from the database system.

Elaboration of Physical Data Model: the class diagram obtained by the previous activity has served as a subsidy to do this third and last activity of the analysis, which was the elaboration of the physical data model, the closest artifact of the final database version.

Construction

The Construction was a stage where the development team rescued the rules described in use cases and requirements and transformed them in programs to be executed in the computers. This construction was divided in three activities: implementation of the use cases, implementation of the data base and specification of the test cases.

The implementation of the use cases dealt exclusively with language machine program of the whole logical described in each use case, and the implementation of the data base contemplated the creation of the physical data base.

On the other hand the specification of the test cases dealt with the logical sequence of steps to run the test of the programs and data base implemented.

Test/Simulation

As to the last stage of the development of VISAO,

Chart 1 – Outbreak and Epidemic Alert Message Contents

Generated Epidemic Alert	Generated Outbreak Alert
Alert Code: E000000070	Alert Code: S000000067
Suspect Disease Code: 1	Suspect Disease Code: 1
Suspect Disease Name: MENINGITIS (MGTE)	Suspect Disease Name: MENINGITIS (MGTE)
Number of Cases: 3	Number of Cases: 2
City Code: 2413003	City Code: 2413003
City Name: São Vicente	City Name: São Vicente
Vaccine Number: 313395	Vaccine Number: 313395
Receiver Code: 1 - 2	Receiver Code: 1 - 2
Emails: aquino.silva@globo.com - zapaw@uol.com.br	Emails: aquino.silva@globo.com - zapaw@uol.com.br

Tests and Simulation covered two activities: the functional tests with fictitious data and simulation with real data. Figure 2 presents the flow which covers both activities.

The execution of functional tests and simulations were based on a sequence of steps described in templates of test cases as well as in file type XML – Extensible Markup Language, which contained fictitious data (for tests) and real data (for simulation) of notification of meningitis, organized by geographical region, type of disease, transmissibility period and incubation period, among other variable.

These files were made available in a standard folder so that VISAO system can read them when executed. Each execution used one or more XML file and generated resulting files containing the execution log.

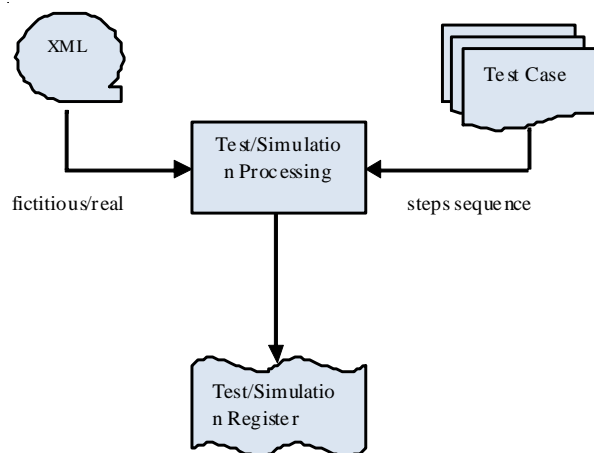With this history in hand, it was created a test register describing the performance of the executions.

Figure 2 – Test/Simulation Execution Flow

For the simulations real cases from data notification were used. They occurred in 2006 in São Paulo State, Brazil. These notifications refer to meningococcal meningitis classified as meningitis outbreaks and were obtained from the CVE – SP.

The first outbreak occurred in the district of Grajaú – São Paulo, community of Sucupira in 2006[10], confirming 3 cases of meningococcal disease with 2 deaths.

The second outbreak occurred in 2006 in the city of Estrela D'Oeste – São Paulo[11], and confirmed 3 cases of meningococcal disease and 2 deaths, with fast and progressive development and identified as meningococcal serogroup C in all 3 cases.

It is important to observe that for the execution of the simulation of the cases above mentioned, VISAO rules were implemented according with the concepts used by CVE – SP, as follows[11]:

Suspected case: all patients with signals or symptoms of acute meningitis, i.e., fever, vomiting, intense headache, nuchal rigidity, with or without change in the mental status; erythematous, macular or petechial rash is also considered, as well as epidemiological information, to characterize a case

supposed to be meningitis.

Confirmed case: suspected case with laboratory confirmation criteria or necropsy.

Outbreak: occurrence of three or more cases confirmed or arising from the same serogroup, in a period minor or equal to three months, that live in the same geographical area but have no direct communication (non related cases).

Besides the adoption of theses concepts, a seven day period was defined for the incubation period and seven days for the transmissibility.

RESULTS

The results of this first pilot study for VISAO can be classified in three categories: (a) creation process results; (b) test execution results; and (c) simulation execution results.

Although the most relevant results of this work are related to simulations, it is worth describing briefly the products obtained during the developing process, as well as the results of tests which the system was submitted.

About the Creation Results

The creation process, which has focused 3 big stages of the project – Inception, Analysis and Construction, generated the following artifacts: 51 requirements specifications, 19 use cases specifications, one use case diagram, one class diagram, one physical data model, 10 procedures, five scripts and two executing programs.

Although they all were indispensable to built up VISAO, the requirements specification and the requirements of use case specification were fundamental for the understanding of rules, restriction and concepts involved with the notification control and alert issuing.

Chart 2 presents the resume of the main requirements and use cases elicited in the Inception stage.

About the tests results

The test process execution represented an important step in the logical and physical validation of VISAO. The following artifacts were generated: seven test cases, five test register, 16 fictitious XML files in first stage, and 10 fictitious XML file in second stage. Such artifacts permitted to realize 74 test process executions with fictitious data.

It is important to highlight that the stage test managed to evidence in its 74 execution inconsistencies not only in code programming and in data base implementation, but also in theoretical conception of the system. The most revealing inconsistency detected was probably the rule of "Group Classification" that deals with the notification related to contact or geographical position, which sowed to be important and vital in context with the issuing of alerts. This rule was created after more than 50% of the tests were performed.

Chart 2 – Summary of Main Requirements and Use Cases of VISAO

Name	Description
Include Notification	The system must permit the inclusion of notifications in two different stages: the first, which register suspect disease data, of patient and respective contacts; and the second, that are input information about classified disease in laboratory.
Treat Included Notification	The system must treat the included notification, observing the active notification history, disease code, geographic position and transmissibility period. If the number of notifications is above the limit (the last included + previous ones), the system must issue an outbreak alert or an epidemic.
Exhibit Macro Alert Notification	The system must be able issuing an alert (by e-mail) containing some information as suspect disease name, number of cases, city name, incidence, vaccine doses, and others.
Deactivated Notification	The system must deactivated automatically a notification, when the incubation and transmissibility period is finished, concerning to the specific infectious disease.
Deactivated Alert	The system must deactivate automatically an outbreak or epidemic alert if all the notification linked to it, were deactivated too.

About Simulations Performance

The simulation was the fourth and last stage that closed the construction process of VISAO and permitted to verify the system behavior with real data of meningococcal meningitis notifications. It is important to note that at this stage, VISAO was configured to produce an alert of outbreak in the occurrence of at least three not related cases of meningococcal meningitis according to CVE – SP[11] and Ministry of Health rules[12].

Grajaú Simulation

Figure 3 presents the results of real data simulation supplied by CVE – SP, related to Meningococcal Meningitis occurred in July 2006 in the Administrative District of Grajaú[10].

The simulation was run as follows:

Case 1 treatment

a) It was created a XML file containing the data notification of case 1 (Chart 3);

b) This file was made available in a folder for treatment;

c) VISAO read the information contained in the XML file and processed them;

d) As there were not sufficient notification for issuing an alert (minimum of three notification), the system did not issue any alert;

e) The system registered the notification of case 1 in the data base and finished the treatment.

Case 2 treatment

a) It was created a XML file containing the data notification of case 2 (Chart 4);

b) This file was made available in a folder for treatment;

c) The system read the information contained in the XML file and processed them;

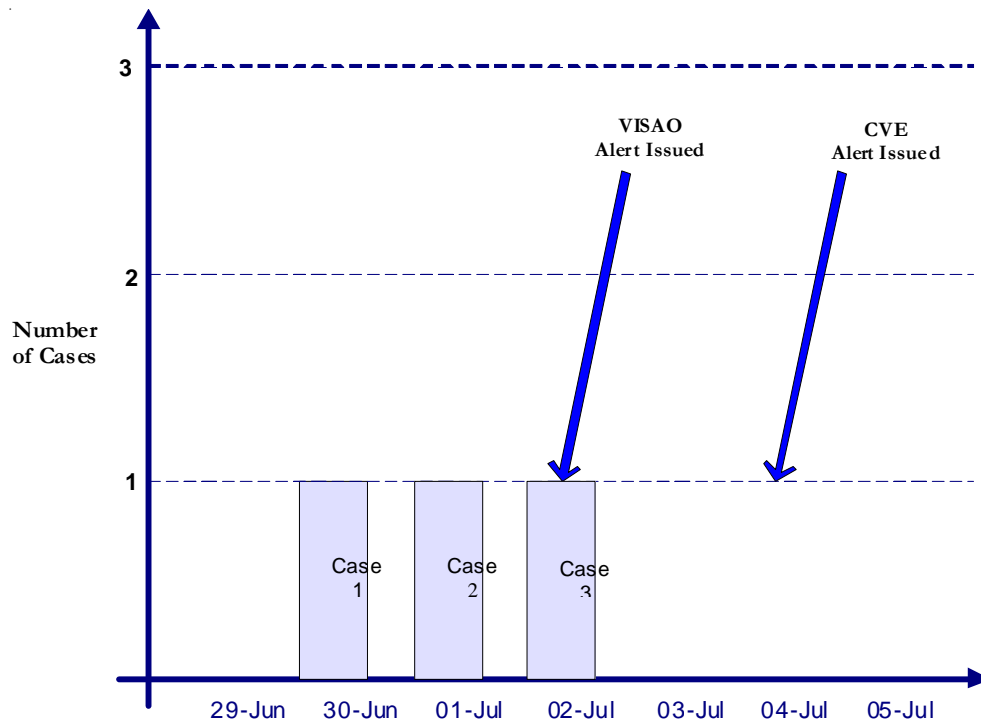d) As there were not sufficient notification for the

Figure 3 –Meningococcal Meningitis Outbreak in Grajaú, 2006

issuing of an alert (minimum of three notification), the system did not issued an alert;

e) The system registered the notification of case 2 and finished the treatment.

Chart 3 – Case 1 Data Notification – Grajaú

```
City Code: 10615844;
Suspect Disease Code: 01 (Meningococcal Meningitis);
Notification Date: 01/07/2006;
First Symptoms Date: 30/06/2006;
Patient Fictitious Name: E.S.P.;
Address Fictitious Patient: XXXXX St. 100
```

Chart 4 – Case 2 Data Notification – Grajaú

```
City Code: 10615844;
Suspect Disease Code: 01 (Meningococcal Meningitis);
Notification Date: 02/07/2006;
First Symptoms Date: 01/07/2006;
Patient Fictitious Name: G.A.S.;
Address Fictitious Patient: YYYYY St. 110
```

Case 3 treatment

a) It was created a XML file containing the data notification of case 3 (Chart 5);

Chart 5 – Case 3 Data Notification – Grajaú

```
City Code: 10615844;
Suspect Disease Code: 01 (Meningococcal Meningitis);
Notification Date: 02/07/2006;
First Symptoms Date: 02/07/2006;
Patient Fictitious Name: M.M.G.;
Address Fictitious Patient: ZZZZZ St. 120
```

b) This file was made available in folder for treatment;

c) VISAO read the information contained in the

XML file and processed them;

d) As there were a sufficient number of notification for the issuing of an alert (minimum of 3 notification), the system **issued an outbreak alert** (Chart 6) in 02/07/2006, **two days before** the formal alert produced by CVE – SP in 04/07/2006;

Chart 6 – Outbreak Alert Message Content issued right after the Case 3 Notification treatment – Grajaú

```
Outbreak Alert Generated – 02/07/2006
Alert Code: S000000068
Suspect Disease Code: 01
Suspect Disease Name: MENINGOCOCCAL MENINGITIS
Number of Cases: 3
City Code: 10615844
City Name: São Paulo
Receiver Code: 1 - 2
E-mails: aquino.silva@globo.com - zapaw@uol.com.br
```

e) The system registered the notification of case 3 in the data base and finished the treatment.

Estrela D'Oeste Simulation

Figure 4 presents the real data simulation of data supplied by CVE – SP, related to outbreak of meningococcal meningitis occurred in September 2006 in the city of Estrela D´Oeste[11].

The simulation contemplated a similar sequence as presented before.

DISCUSSION AND CONCLUSION

Infectious diseases are still a threat for world populations even considering the improvement experienced since vaccination, sanitary condition and therapeutical developments in the last 50 years.

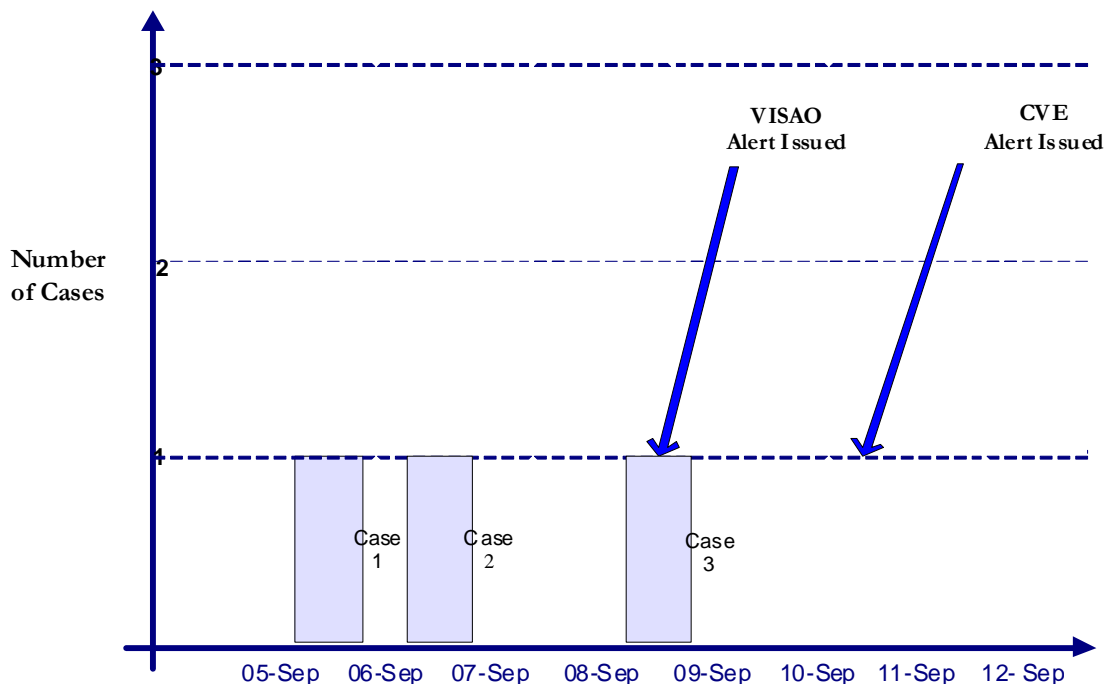Meningitis is a special chapter of infectious disease,

Figure 4 – Meningococcal Meningitis Outbreak in Estrela D'Oeste City - 2006

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besides possessing different etiologies and resulting in distinguished aspects related to public health, it needs a diversified strategy of prevention and control[13].

In 2003 the number of cases notified reached 2.923. The disease outbreaks throughout Brazil are common, as for example the occurrence in São Joaquim da Barra[14] in 2004, in São Paulo (Grajaú)[10] and Estrela D´Oeste[11] in 2006, and again in São Paulo (Ipiranga)[15] in 2007.

The Ministry of Health, within the various strategies established, has invested in the strengthening of the capacity of cities and states for quickly detecting suspecting cases and adopts effective blocking measures, besides increasing routine and uniform vaccine coverage and adopting specific strategies like door-to-door vaccination, intensification of vaccine campaign. The Ministry of Health also suggests a better integration within the surveillance and control bureaus in assisting health offices, once the principal target of the action is focused on the diagnosis and treatment of sick people and immunization of contacts, aiming the interruption of the transmission chain.

In respect to governmental action related to technological platform, maybe the creation of SINAN[6], although fundamental in helping to analysis epidemiological data, was not enough to optimize the control actions because it is not a real time outbreak alert generator.

VISAO fits in this technological gap, whose principal characteristic is to detect and precociously inform the occurrence of an outbreak or epidemic of an infectious disease, presently shaped specifically to treat the notification of meningococcal meningitis.

Classified as an *EWARNS*[16], VISAO can not foresee an outbreak, but can manage to detect it quickly, as soon as the minimum number of case notification reaches its data base. This was shown in simulations run in real outbreak case of meningitis in Grajaú and Estrela D´Oeste in which VISAO anticipated in communicating the occurrences as compared to the current information flow of CVE – SP.

Although we do not have information about the causes, the fact is the outbreak information was known

only two days after, on July 4th 2006. Two days may be not a too long delay to start up an appropriated epidemiological control. However, whenever it deals with high lethal disease and easy transmission, any time saving is fundamental to avoid the quick expansion of the disease and consequently, reduce to the maximum death statistics within the population and related economic and social costs. To reach the efficiency above mentioned, VISAO has been developed under an architecture that uses two fundamental mathematical that uses early detection: the signal detection theory[17] and the decision theory[18]. In general terms, signal detection is summarized in interpreting as a signal, the occurrence of certain event, for example, the occurrence of three cases of meningitis meningococcal simultaneously in time and in the same geographical area. The decision theory refers to mathematical formalism used to obtain the three more adequate detection characteristics to a given application: sensitivity, specificity and timeliness. Maintained under its architecture, the two theories help VISAO system to be classified as a genuine early detection system and to outstand as an active system for issuing alerts of infectious disease as initially proposed. On the other hand, developing a computing system for infection control to countries is not a simple task. The obstacles that arises along the developing process, implementation and utilization of the system, starts from the lack of basic infrastructure to introduce the system in each heath center and the potential rejection of the system by the users. The first challenge already overcome by our group when developing VISAO was the inception stage of the system, due to the complexity of rules formalization about the events and parameters related to the infectious disease and corresponding alerts. It is important to remember that independent of the acceptance of a system, the subnotification of cases[19] may turn to be a serious problem for surveillance. A system like VISAO must integrate a strategic plan for infection surveillance and control centers, so that it will not sound like an additional system to the existing ones, avoiding the perception to the users of having to do an extra task among their quotidian work.

REFERÊNCIAS

1. USA. Environment News Service. World Health Officials Agree to Report All Major Disease Outbreaks. 2005. Available on http://www.ens-newswire.com/ens/may2005/2005-05-20-01.asp, accessed 05 July 2005.
2. WHO. The world health report 2007: a safer future: global public health security in the 21st century. Geneva, Switzerland, 2007.
3. Brazil. CVE. Cases confirmed, Incidence Coeff. (by 100.000 hab.), Deaths and Lethality of the State of São Paulo – 1992 to 2008, São Paulo, 2008.
4. Fonseca, C., Moraes, J. C., Barradas, R. B., The meningitis book: a disease in the light of the city. 1st ed. São Paulo: Segmento Farma Editor, 2004.
5. Carvalhanas, T., Epidemiological Situation of Bacterial Meningitis in São Paulo State. Bepa 2004; 05: 4-7 1.
6. Brito, H. M., Vassoler, G. L., Bortolon, S., Arantes, D. O., A Hierarchy of Geoepidemiological Data Servers using GML, In: VIII Brazilian Congress of Information Technology in Health, 2002, Natal, Annals of VIII Health Information Brazilian Congress, Natal, 2002.
7. National Press. National Disease Report of Compulsory Notification. Brasília: Official Diary of Union, 2006.
8. Alencar, F. M. R., Mapping the Organizational Modeling in Precise Specification. [PhD Thesis]. Recife: Informatics Center, University Federal of Pernambuco, 1999.

9. OMG. Unified Modeling Language: Superstructured. Available on http://www.omg.org/docs/formal/07-02-03.pdf, accessed 23 December 2007.

10. Ciccone, F. H., et al., Meningococcal Disease: Outbreak Investigation Community Administrative District of Grajaú, City of São Paulo, July 20. BEPA 2006; 31: 7-12 1.

11. Fernandes, F. C., et al., Meningitis Disease Outbreak in Estrela D'Oeste City, SP, September 2006: from investigation to control. BEPA 2007; 37: 2-9 4.

12. Brazil. Ministry of Health. Epidemiological Surveillance Guide / Ministry of Health, Health Surveillance Secretary. 6th ed. Brasília: Ministry of Health, 2005.

13. Moraes, J. C., Barata, R. C. B., History of Medicine: the epidemic that dictatorship couldn't hide. 33rd ed. São Paulo: Cremesp Magazine, 2005.

14. Pellini A. C. G., et al., Viral Meningitis Outbreak Investigation – São Joaquim da Barra City (SP), February to April 2004. Bepa 2004; 7: 7 – 11 1.

15. Fernandes, R. M. B. P., et al., Outbreak Investigation Community, Administrative District of Ipiranga, city of São Paulo, July 2007, Bepa 2007; 44: 10 – 17 4.

16. Cger, D., Under the Weather: Climate, Ecosystems, and Infectious Disease. Washington, D.C.: National Academy Press, 2001.

17. Kay, S., Fundamentals of Statistical Signal Processing: Detection Theory. New York: Prentice Hall, 1998.

18. Morgenstern, O., von Neumann, J., Theory of Games and Economic Behavior. 2nd ed. Princeton: Princeton University Press, 2007.

19. Miranzi, S. S. C., Temporal tendency analysis: an alternative to evaluation of vaccination impact against Haemophilus influenzae type b, in Brazil [PhD Thesis]. Ribeirão Preto: Ribeirão Preto Nurse School, University of São Paulo, 2004.