Time is safety: 
Point-of-Impact testing and real-time typing

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The pandemic influenza
Influenza during pandemic 2009
UMCG versus The Netherlands
Usefulness of Molecular Detection

- Useful for viruses that cannot be grown at all, or during acute infections when serology has limited value (respiratory infections).
- Follow-up of viral load during antiviral treatment. Best examples are HIV-1/2, HBV and HCV, but also CMV and EBV as more and more antivirals do become available.
- Best characterization of viral genome, to determine mutations related to resistance, or to determine viral genotype.
- No more a research tool, but daily practice in larger laboratories. Important in transplantation setting, outbreak management.
- Fast turn-around-time possible to make decisions while the patient is still at the Emergency Station.
Use of molecular data in surveillance

• Use of molecular data to confirm outbreak already suspicion based on place, time, person

• Molecular data incorporated in routine surveillance (laboratory based surveillance)
  – Monitoring infectious disease trends
  – Evaluate impact of control & prevention measures
  – Detect clusters or relevant changes in pathogen presence and/or behaviour
Use of molecular data in surveillance

- Currently: diagnostic laboratories submit strains or samples to reference laboratories for characterisation and typing
  
  - Noronet
    - to detect trends and identify possible outbreaks (geographical and temporal trends)
      - Genotypes differ in their ability to spread: GII.4
      - Foodborne (non GII) versus human-to-human transmission (GII.4)
    - Antigenic changes
      - Rapid displacement of variants
  
- Typened: enterovirus surveillance
  - Polio-eradication
  - Shift from culture to molecular diagnostics
Typened - Typing Network Netherlands

Typingtool (webservice)
Reference set
Typing algorithm

Lab network
Data sharing
Consensus typing methods
Consensus nomenclature
Coordinator / curator

Analysis modules
Time
Place
Similarity
Phylogeny
Elevations

Analysis submits data
Lab network defines and updates reference sets
Typingtool types sequences
Web database queries database

Public health / research question
Alerts, reports, publications

Case
Sample
Sequence
Typing result

Niesters et al, Euro Surveill. 2013: 18 (4)
But…

• Retrospectively
  – Delay between diagnostic sampling, typing and upload of sequence analysis information
  – Delay in detecting changes

• Lack of clinical and epidemiological data
  – Sequences can be uploaded without clinical information
  – Clinical information mostly lacking at laboratory site

UMCG: focus on clinical and epidemiological data in relation to sequence data:
  - Explain illness
  - Insight in transmission routes
  - Value of control measures
Connectivity between regional centers
(does not cross borders)
Genotypes of detected norovirus

448 norovirus positive samples
334 patients, 398 disease episodes (sample date > 1 week apart)
Symptoms norovirus in different settings

- Fever
- Vomit
- Diarrhea

Sources of clusters:
- HA-infection
- CA-infection

- p=0.002
- p=0.005
- p=0.02
Symptoms norovirus versus rotavirus

- Fever: p<0.001
- Vomit: p=0.04
- Diarrhea: Norovirus (n=132) vs Rotavirus (n=69)
- Abdominal pain
- Less urine
What do we want to know?

“Next generation epidemiology”: spatial-temporal-molecular

- Insight into transmission
  - Probability of patient to patient transfer of specific virus strain
    - Coincidence that patients have the same virus?
    - Repeated introduction from outside the hospital?
    - Real clustering/outbreak?
  - Role personnel and visitors

- Effect of infection control measures on transmission

- Real-time sequencing:
  - Further characterization norovirus, parechovirus, enterovirus, rhinovirus immediately after detection by using sequence analysis
Outbreak on a Paediatric Oncology ward

First five patients, four different types:

- **P1 and P3**  II.4 2009
- **P2**  II.7
- **P4**  II.b
- **P5**  II.2

**P7** non-typable

Additional measures: environment, education, handrubs, excluding ill staff from work, cohorting staff

First patient was admitted with complaints of norovirus infection.

Following patients were hospital acquired!
What do we want to know?

- **“Next generation epidemiology”: spatial-temporal-molecular**
  - **Insight into transmission**
    - Probability of patient to patient transfer of specific virus strain
      - Coincidence that patients have the same virus?
      - Repeated introduction from outside the hospital?
      - Real clustering/outbreak?
    - Role personnel and visitors
  - **Effect of infection control measures on transmission**
  - **Regional surveillance!**
    - Northern region of the Netherlands, Dutch/German border (Euregio)
      - German virological surveillance Cologne
    - General practitioners, other hospitals
TYPENED and REGIOtype

- Sequencing of enterovirus, parechovirus, rhinovirus and norovirus in the region and in real time
Norovirus II.4.Sydney
Norovirus II.4.2009
To conclude

- The benefit of molecular diagnostics is more than just detection and characterisation of a target
  - Understanding disease
    - Explain illness
    - Importance of quantitative data: more virus more illness?
  - Epidemiology and infection control
    - Transmission routes and sources of infection
    - Value of infection control measures

- We need to understand the benefit of faster results
  - Faster results, point-of-care, have a benefit for disease management, infection control and cost-reduction (€/hr concept)
Application of molecular techniques into the epidemiology of enterovirus D68
• Bronchiolitis-type illness
• Some severe cases requiring intensive care treatment
• Many patients had underlying condition
Explaining illness: EV68

August-November 2010: 24 patients with only EV68 detection

‘RS-like illness’

In same period: peak in EV68 detections in sentinel surveillance system into respiratory illness among patients seen by general practitioner; upsurge of EV68 in USA, Japan and other countries worldwide
Enterovirus D68 outbreak 2014

- Children (<16 years)
- 68% had prior history of wheezing
- Nearly all patients required intensive care treatment
- Many reports from other states and Canada
- Testing (sequencing) at CDC: only severe cases
Summer 2014 in UMCG

<table>
<thead>
<tr>
<th>Genotype</th>
<th>number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV-D68</td>
<td>17</td>
</tr>
<tr>
<td>CV-A6</td>
<td>11</td>
</tr>
<tr>
<td>E-16</td>
<td>6</td>
</tr>
<tr>
<td>CV-A2</td>
<td>4</td>
</tr>
<tr>
<td>CV-A4</td>
<td>4</td>
</tr>
<tr>
<td>E-25</td>
<td>3</td>
</tr>
<tr>
<td>E-18</td>
<td>2</td>
</tr>
<tr>
<td>CV-B3</td>
<td>2</td>
</tr>
<tr>
<td>CV-A16</td>
<td>2</td>
</tr>
<tr>
<td>EV-C104</td>
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<tr>
<td>EV-C105</td>
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<tr>
<td>E-3</td>
<td>1</td>
</tr>
<tr>
<td>CV-B4</td>
<td>1</td>
</tr>
<tr>
<td>CV-B1</td>
<td>1</td>
</tr>
<tr>
<td>CV-A10</td>
<td>1</td>
</tr>
<tr>
<td>CV-A11</td>
<td>1</td>
</tr>
<tr>
<td>ND</td>
<td>14</td>
</tr>
<tr>
<td>TBA</td>
<td>4</td>
</tr>
</tbody>
</table>
**Epidemiological curve**

- **Number of EV-D68 positives**
- **Week**
  - 27 to 48
  - **July 1st**
  - **ESCV 2014, Prague**
  - **December 1st**

*17 samples are not included in this graph, due to a lack of sampling date*
European detection rates per country

- 42 laboratories from 18 countries
- 17,248 samples tested
- 389 EV-D68 positives
Are we connected?
Colors represents the country of origin.
• In USA 2014: EV-D68 outbreak
• In Europa circulation of same EV-D68 genotypes
• Different approach of diagnostics for viral infections gives a different picture in different countries

How do we take care that “emerging viruses” do become detected?
From Regiotype to TypeNed to Eurotype?

Europe must be more united!
The silver generation
Point-of-Impact:
From Classical PCR to Point-of-Impact Systems.

Target: respiratory viruses
point-of-impact

IQuum
The lab in a tube technology

GeneXpert Infinity System

Biocartis platform

FilmArray, bioMerieux

Luminex Aries

GenMark Dx
Why I call it Point-of-Impact
(and not Point-of-Care)

• We are at the initial introduction phase of new systems that enable rapid molecular testing. Rapid implies near bedside testing or while the patient is still waiting for the results (emergency room, out-of-office post).

• The new rapid molecular assays are still “in development” and quality indicators are not always defined (like what is an acceptable clinical detection limit). Most of them are qualitative.

• Important is clinical support related to the interpretation of the results.

• POC testing also implies compliant with ISO22870:2006 in combination with ISO15189:2012. Excluded is self-testing in a home or community setting.
A respiratory season is dynamic!
Introduction: what happened first

- The Influenza season of 2012-2013 was characterized by co-circulation of two Influenza A types.
  - H1N1 2009pdm09
  - H3N2

- Due to the circulation of two Influenza viruses Influenza A-positive patients had to be admitted into single rooms.

- Rapid testing for influenza using an antigen based test had a low sensitivity.

- A large number of different respiratory viruses were circulating during a long (5 months) period of time, with RSV and influenza viruses being present simultaneously.
Number of viruses identified
December 2012-April 2013

A total of 1259 respiratory samples were tested
166 patients had Influenza A
• 59 had H1N1pdm09
• 104 had H3N2
• 3 NT
Isolation regimen of patients admitted with a respiratory illness.

- **Neg**
- **Infl A**
- **Other virus**

- **No isolation**

- **Genotype?**

- **H1N1**
- **H1N1**
- **H1N1**
- **H1N1**

- **Care in cohort**

- **H3N2**
- **H3N2**
- **H3N2**
- **H3N2**

- **Care in cohort**
## Overview (virology)

<table>
<thead>
<tr>
<th>Category</th>
<th>Throughput</th>
<th>Testing Method</th>
<th>Turnaround Time</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>High throughput</td>
<td>Sample in-result</td>
<td>Commercial</td>
<td>Commercial</td>
<td>Blood screening</td>
</tr>
<tr>
<td></td>
<td>out</td>
<td>Blood screening</td>
<td>STD</td>
<td>HPV</td>
</tr>
<tr>
<td>Medium to low throughput</td>
<td>In-house or LDT</td>
<td>“Everything”</td>
<td>Commercial</td>
<td>Limited portfolio</td>
</tr>
<tr>
<td>Point-of-Care</td>
<td>Commercial</td>
<td>Short TAT</td>
<td>Influenza virus</td>
<td>Sample in - result out</td>
</tr>
<tr>
<td>Point-of-Impact</td>
<td>Commercial</td>
<td>Influenza virus</td>
<td>Norovirus</td>
<td>Respiratory viruses</td>
</tr>
</tbody>
</table>

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Point-of-Impact testing in the emergency department: diagnostics for respiratory viral infections.
Season 2014-2015
The challenges at the Emergency Department

- Experience from previous years was that samples from patients received at the end of the day, on Friday (after 16.00 hr) and in the weekend, had a long TAT.

- The respiratory season of 2014-2015 was characterized by a large diversity of different respiratory viruses circulating during a long (5 months) period.

- Make a discrimination between infection and rejection in Tx patients (long-Tx e.g.).

- Lack of isolation rooms.

- Request for data on more viruses that circulated simultaneously.
The solutions

• Extend service hours 7 days a week from 8 till 22 hr.

• Select a POI-test with a short TAT. In our case the BioFire FilmArray.

• Be sure to include not only Influenza virus and RSV!

• Agreement between clinical departments servicing the Emergency Department (ED) and the Clinical Virology Division, to improve the diagnostic service by selecting early in the ED-process those critical ill patients due to most likely a viral infection, and take samples at this early stage.

• We know from an ED-LEAN-project that patients stay approximately 4 hours at the ED.
Viruses detected weekly – FilmArray
Season 2014-2015

![Graph showing weekly detections of various viruses](Image)

- Influenza A
- Influenza B
- RSV
- Coronavirus
- Rhinovirus
- hMPV
- PIV

**Number of infections**

**Week**

**Influenza RSV only**
Turnaround time ED
from patient registration (ED) till diagnostic request (virology)
Turnaround time virology
from diagnostic request (virology) till feedback of the result

- <2h: 59%
- <3h: 93%
- >3h: 7%

Number of tests vs. minutes

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Total Turnaround Time
= from patient registration (ED) till feedback of the result

- <3h: 59%
- <4h: 83%
- <5h: 93%
- >5h: 7%
Total Turnaround Time
Focus for improvement

- <3h: 59%
- <4h: 83%
- <5h: 93%
- >5h: 7%

Number of tests vs. minutes

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ESCMID Online Lecture Library
Dear Dr. Knoester, FilmArray 2 detected Influenza A, Influenza A/H1 in sample E2014100465
Diagnostic policy 2014-2015
Respiratory viral infections

Mean length of stay at the Emergency Department: 4h and 27 min

Mean total turnaround time of diagnostics: 3h and 14 min

17h

Mean turnaround time: 1h and 12 min

Patient with suspected respiratory viral infection → Sampling in early triage and dispatch to laboratory → Nurse; Co-assistant

36h

Department of Medical Microbiology
Division of clinical virology

19h

Mean turnaround time: 2h and 2 min

Technician → Performing the POI test

Technician; Medical virologist → Interpretation of test results

Diagnosis; Positioning; Treatment plan

Physician

Admission; Treatment
Is this affordable point-of-impact?

- GeneXpert Infinity System
- Biocartis platform
- IQuum: The lab in a tube technology
- FilmArray, bioMerieux
- Luminex Aries
- GenMark Dx

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Cost Effectiveness of **AID**-Stewardship
The **AID**-Stewardship Portfolio

- [Antibiotic/Antimicrobial Stewardship](#)
- [Infection Control Stewardship](#)
- [Diagnostic Stewardship](#)

Determine and communicate the value of molecular diagnostics!

- Take the lead (use of POC/POI; E-health)
- Cost effectiveness
- Awareness (communicate)
The € hour concept
(comparable with kWhr)

• Time-to-result or turn-around-time (TAT) for critical care is important.

• Time-to-result for decision making is important.
  • Start or stop treatment
  • Isolation of patient or not
  • Cohorting of patients
    (e.g. Influenza H1 infected patients in one room)
  • Patient can go home

• Combine time-to-result with costs of assay. The €hr
  — We call this benefit
How to calculate benefit?

- Time-to-result or turn-around-time (TAT) for critical care is important.

- The most important stakeholder is the PATIENT.

- Factors to consider LDT compared to POI testing
  - Costs per result
  - Additional personnel costs
  - Avoiding unnecessary isolations or placements outside the hospital (Negative results are extremely valuable!)
  - Reducing nosocomial infections due to rapid TAT
  - How to calculate money that you don’t spend?
The €hr concept
(641 request from ED and 492 complete sets of data)

• POI for testing Clinical Virology Department only

• LDT (old situation)
  – POI value: Range 1,226K-1,974K €hr or 2,493-4,013 €hr per result

• FilmArray (new situation)
  – POI value: 180,194 €hr or 366 €hr per result

• **POI FilmArray benefit is 6.8 – 10.96 times that of LDT**
  – Assuming equal clinical value/characteristics!
The €hr concept
(641 request from ED and 492 complete sets of data)

• Costs Clinical Virology and Emergency Department

• LDT (old situation)
  – Mean total TAT at diagnostic department: 36 hours

• FilmArray (new situation)
  – Mean total TAT: 3.14 hours

• POI FilmArray benefit will even be higher compared to LDT
How to calculate benefit?

- Factors to consider LDT compared to FilmArray
  - FilmArray: €89,205
  - No LDT and no LDT typing: €64,570–€103,930
  - Extra personnel costs: €8,905
  - Due to rapid TAT, we avoided 181 isolations (negative FilmArray result): €154,806 not spend (€855 per bed per day)?!
  - Benefit reducing nosocomial infections (factor 0.233–0.206), costs per nosocomial infection €11,240 (Jacobs et al, 2013): €37,024
  - Unknown costs for not sending patient to other hospital because lack of isolation rooms!

- Total benefit is: €158,290–€197,650 or €323–€401 per result.
The Extended Diagnostic Triangle
Conclusion

• POI testing is implemented for patient care in the ED

• POI testing is cost beneficial!

• Negative results do have an important value and impact

• POI from a diagnostic point of view is 6.8 – 10.96 times higher for FilmArray compared to LDT; even higher if total ED process is included.
Conclusion

• Highlight the need for incorporating molecular diagnostics into routine testing

detection and identification of these viruses could help in explaining serious illness, giving guidance to medical care and preventing unnecessary treatment with antibiotics

• We should investigate what is the real clinical relevance of the “other” viruses, being not influenza and RSV.
Capacity-building Workshop

Whole Genome Sequencing for clinical microbiology and infection prevention

October 12th – 14th, 2016, UMCG Groningen

Organisers
- ESCMID Study Group for Genomic and Molecular Diagnostics
- ESCMID Study Group for Epidemiological Markers
- Department of Medical Microbiology and Infection Prevention (UMCG)

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