NANYANG TECHNOLOGICAL UNIVERSITY

Global Microbial Identifier

Science – Food - Health

The next global break-through: the rise of Next Generation Sequencing

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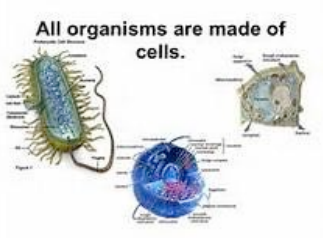
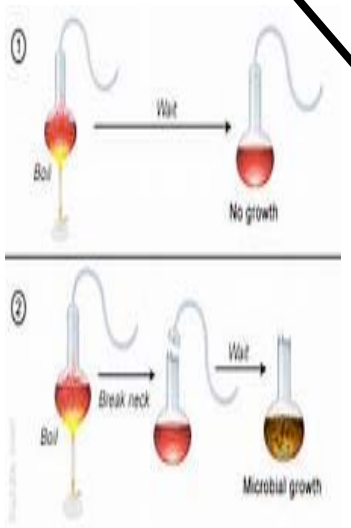
Whole Genome Sequencing (WGS) - The next Milestone

NOTEWORTHY MILESTONES IN MICROBIOLOGY



Schwann– 1839– Cell Theory



Pasteur– 1861– Proves Germ Theory
Initiating identification / pure culture (+ Koch)

2005 – WGS of microorganisms
Understanding microorganisms

Redi– 1668 – Disproves Spontaneous Generation

Paradigm Shift

from Pasteur and Koch to Watson and Crick

"In 5 to 10 years all micro. labs will have a DNA sequencer.. whole bacterial genome might be less than 50 EURO"

The capacity to exchange/manage large data quantities over the web has likewise increased dramatically over recent years

Enabling the potential creation of global databases of DNA-codes of all relevant microbiological strains"

Statement, Expert Meeting Microbiological Genomic Systems, Bruxelles (2011)

**"There is a pathway from good science to publication to evidence, and to programs that work.
In this way research becomes an inherent part of problem-solving and policy implementation"**

Julio Frenk
Former Mexican Minister of Health
Former Assistant Director General WHO
Dean, Harvard School of Public Health

Whole Genome Sequencing (WGS)
Next Generation Sequencing (NGS)
Advantages:

Diagnosis of microorganisms will improve

Outbreak investigation will improve

Surveillance and Prevention will improve

Microbiological Research will improve

Bigger picture – multiple facets

Clinical – the patient will survive only if we have the sequence in our database

Clinical – metagenomic analysis for pathogen detection/identification/characterization

Surveillance – metagenomics in sewage

One Health – linking human and animal pathogens

Food Safety, outbreaks – much earlier, much more efficient

Food Safety, source attribution – which types of food are responsible for sporadic cases

Real economic issue

The cost of disease burden is often not well investigated – and especially not for food related diseases

However, the total cost to society of AMR has been estimated in the USA as:

US$ 20 billion per year (approx. 0.1% GDP)

DNA Forensics of Microorganisms

Genome sequence is agnostic. One biological assay could works on all pathogen species

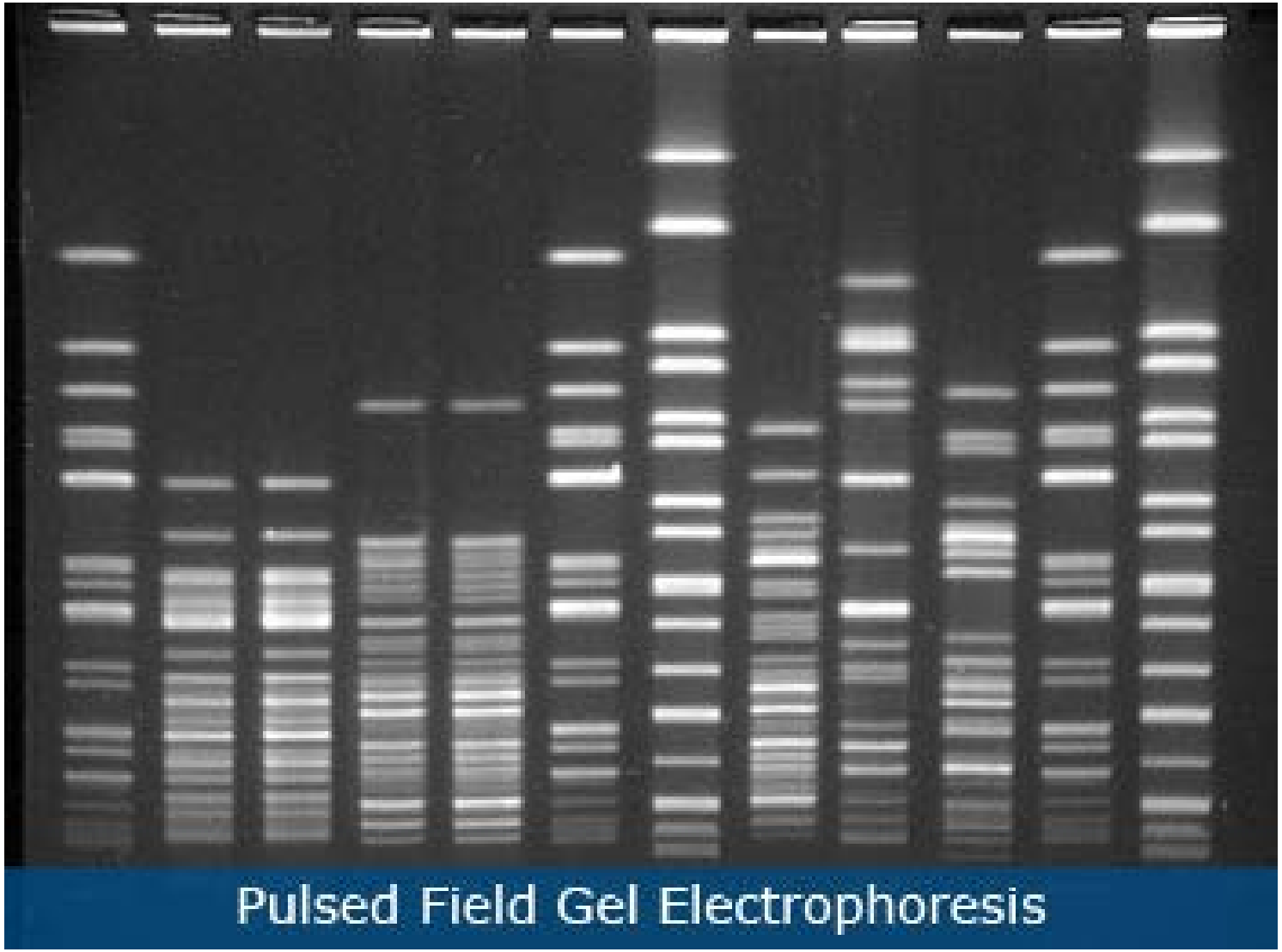
Immediately useful. All we need is the genome and a little metadata.

WGS is now routine in US foodborne outbreak response and compliance/surveillance activities. (FDA, CDC, FSIS)

WGS can be used to inform traceback investigations unlike ever before – numerous offshoot applications exist (i.e., supply chain management, quality assurance, process evaluation, etc.)

A Pathogen Genome Is The Fingerprint

This is what a PFGE slide looks like



This is what a whole genome sequence looks like
(4 million letters for a standard bacterium)

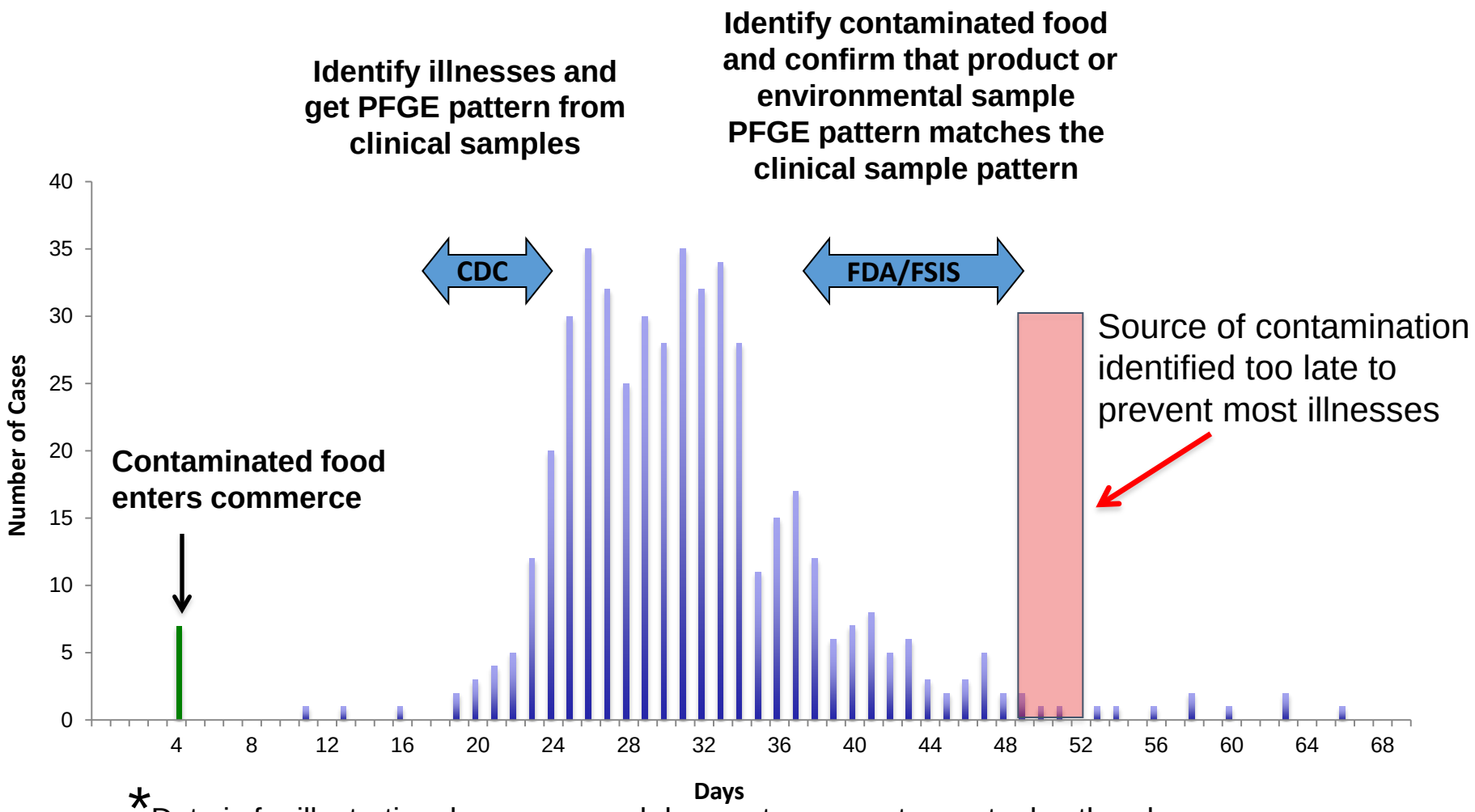
Difference between PFGE and WGS

Comparing two isolates with PFGE is like comparing two books by comparing the length of the chapters of the two books

Comparing two isolates with WGS is like comparing two books by comparing each letter in the two books

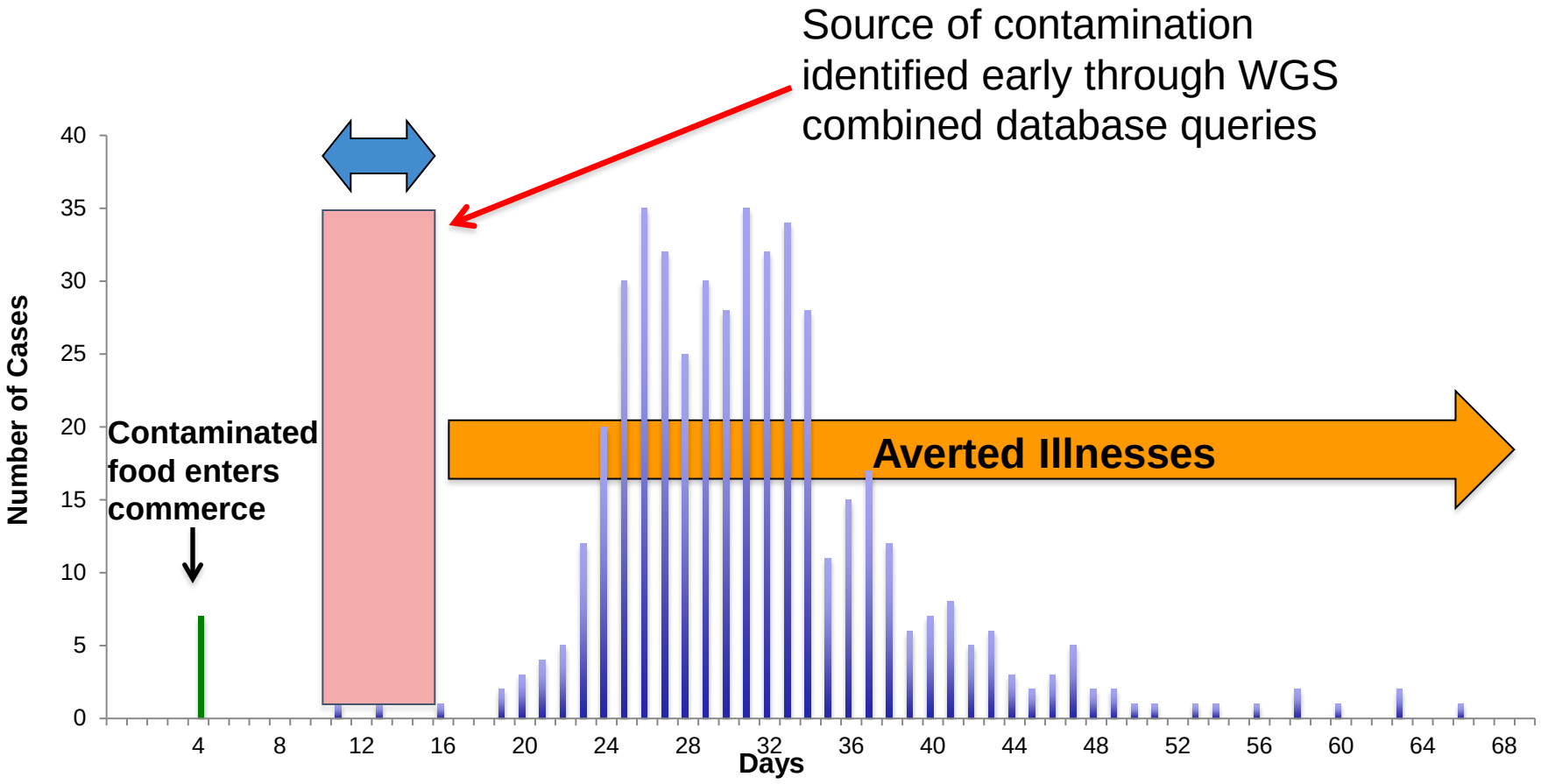
Representative* timeline for traditional approach (PFGE) in the USA system

PFGE: Pulsed Field Gel Electrophoresis



*Data is for illustrational purposes and does not represent an actual outbreak

Representative* timeline using WGS



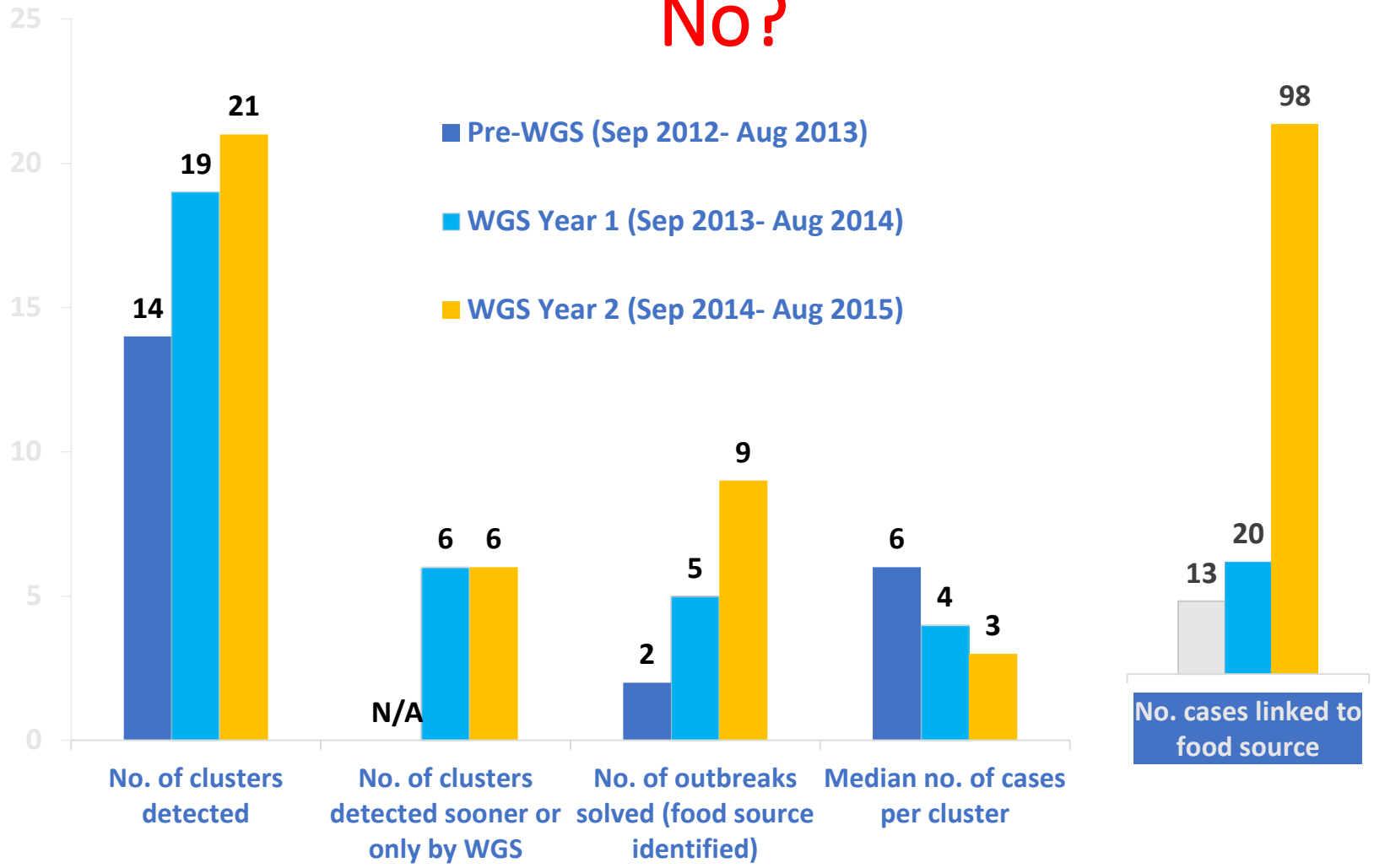
*Data is for illustrational purposes and does not represent an actual outbreak

Listeria Cluster Metrics - Before and After WGS

This should really fire up interest from Food industry

We have a real potential to get to the final solution for the pervasive Listeria problem,

No?



Courtesy: Amanda Conrad, Outbreak Preparedness and Response Branch

One step back – How does all this impact food safety in general (apart from helping in outbreaks)

Although many countries maintain their food safety system is unique:

First, we need to accept:

Most food safety systems operate the same way

The mistakes we make have been repeated again and again

And even if you improve, the mistakes will keep on coming in over the borders

So, Another Example:

Source Attribution

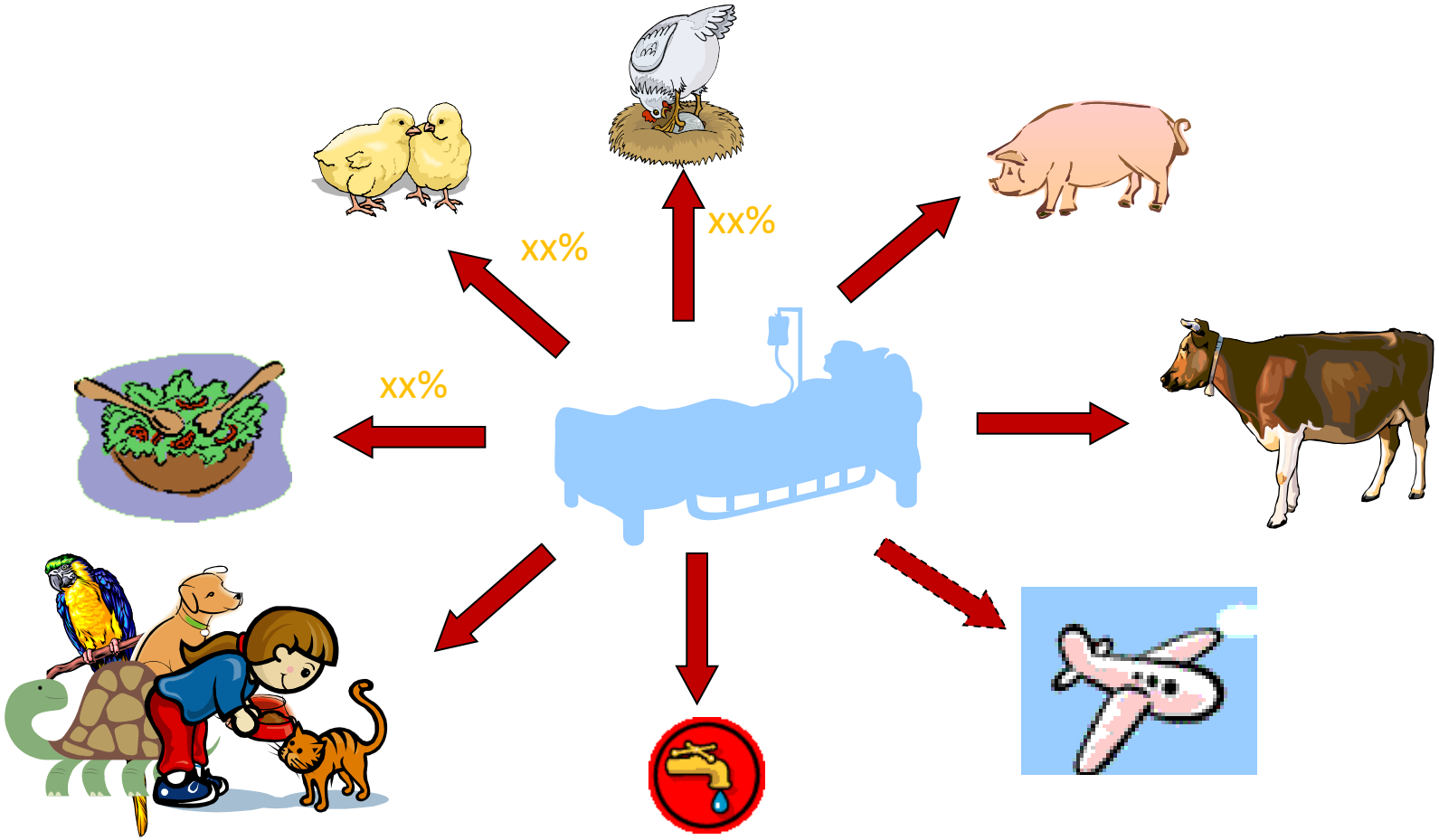
Before WGS: *Salmonella only*

After WGS: *all Microorganisms (potentially)*

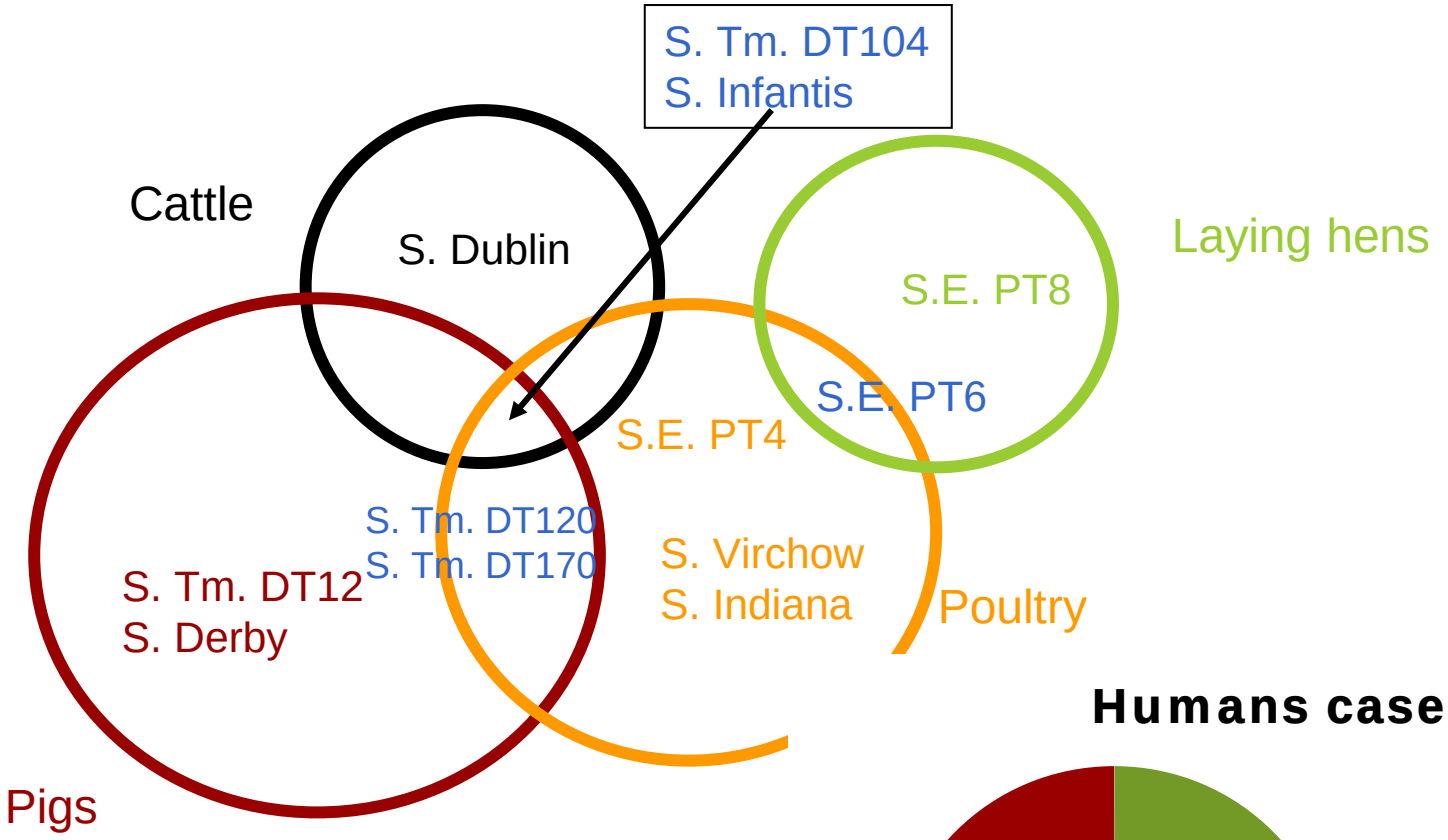
How can typing link lab id. and epidemiology:

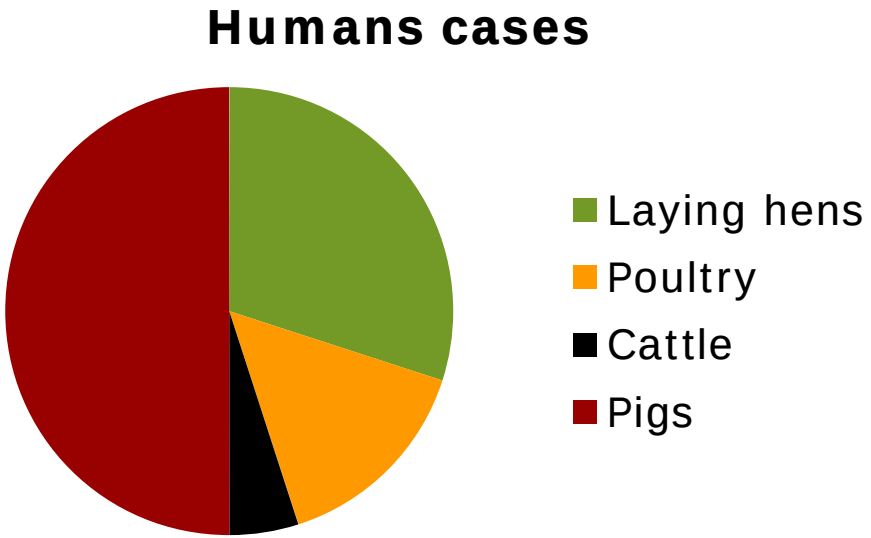
Linking disease and food:

Definition: Source attribution - partitioning human disease burden to specific sources (Pires et al., 2009).

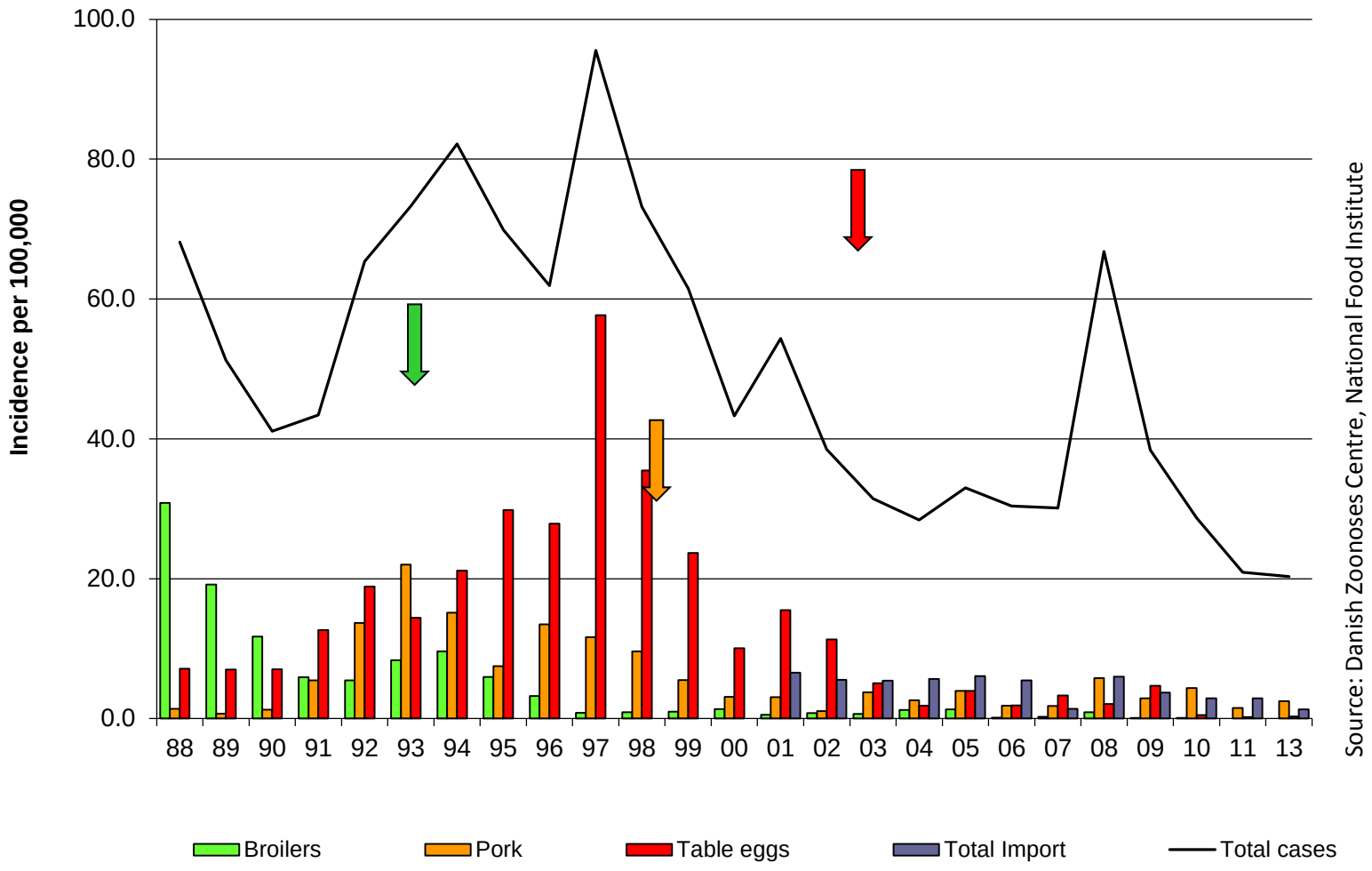


Example:
Salmonella source attribution





Source attribution to guide policy intervention
Salmonellosis in Denmark, 1988-2013



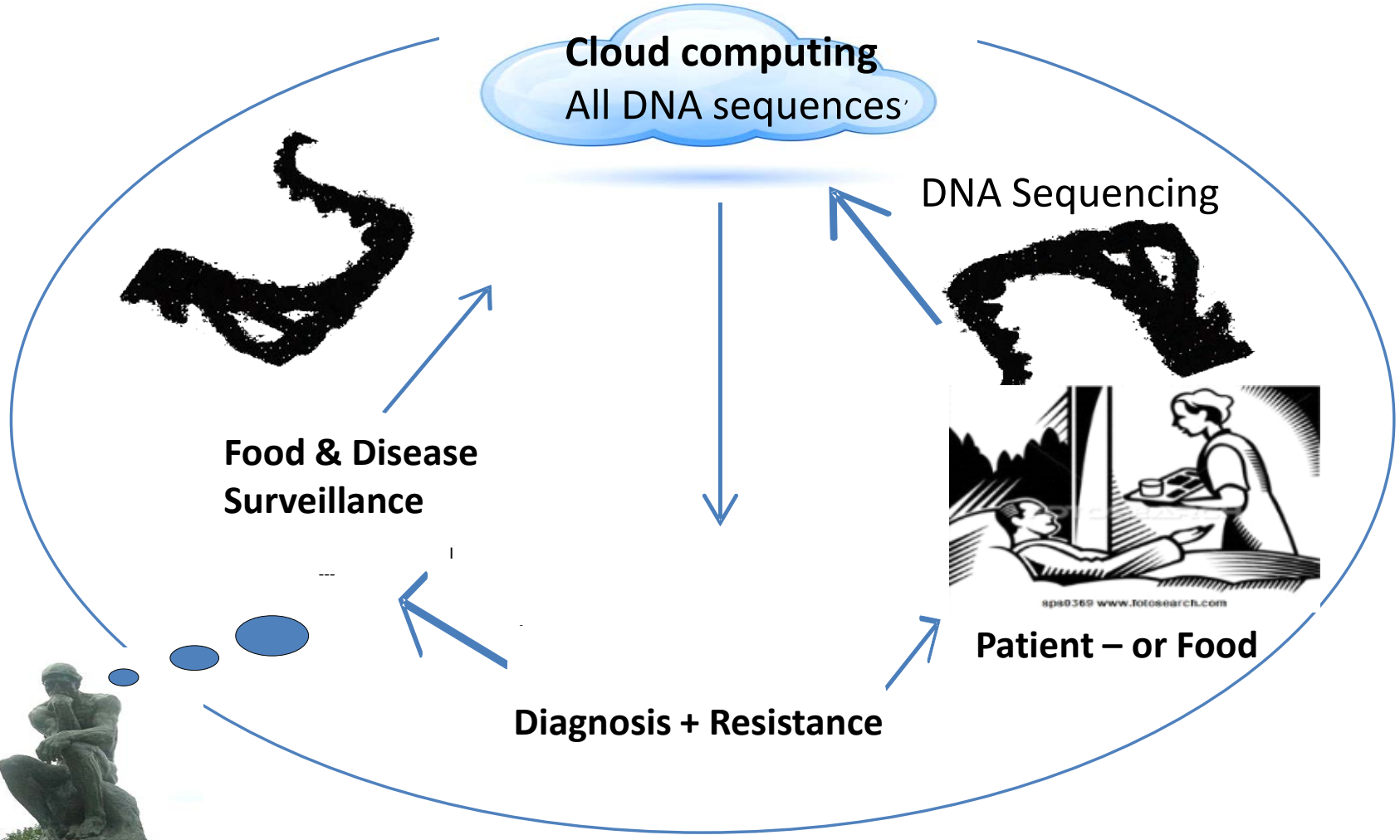
Arrows indicate implementation of sector-specific intervention

Note:

This is not about outbreaks – this is about all cases of foodborne salmonellosis – thus including <u>sporadic cases</u> (constituting 90-95% of all cases)

Global Microbial Identifier – the Idea

1st global tool to identify all Microorganisms and Antimicrobial Resistance



Global Microbial Identifier

GMI - according to the Charter *(see web-site)*

GMI consists of

The Platform

(organizing body, including e.g. the Steering Committee and the Working Groups) and

The Community Network

(all individuals and organizations that subscribe to the GMI Website by filling in a profile)

The Working Groups

Four WGs – originally five

The four GMI Work Groups

- **WG1: Political challenges, outreach and building a global network**
- **Letter to be sent to Governments of the world (primary recipients Ministries of Health), suggesting that WGS discussions at World Health Assembly (WHA) May 2018 and 2019**
- **GMI11 planned for Geneva Week of 14 May 2018 – week before World Health Assembly**
- **WG2: Repository and storage of sequence and meta-data**
- **Epidemiological metadata can now be entered in NCBI via a MS Excel or CSV file, modelled according the Global Microbial Identifier (GMI)/NCBI minimum epidemiological data requirements**
- **WG3: Analytical approaches**
- **International comparability of WGS data for public health surveillance through sharing of standardized data sets, tools, and nomenclature**
- **WG4: Ring trials and quality assurance (Proficiency Testing: PT)**
- **With major input from US FDA and WHO Coll. Centre (Tech Uni DK) prepared PT2017 (the third GMI PT), assessing (1a) the laboratory's DNA sequencing procedures, (1b) the laboratory's sequencing output, (2) procedure to identify variant sites within whole genome sequence data and cluster and distinguish samples based on those variants.**

Virus – Bacteria – Parasites

Same – Same

www.globalmicrobialidentifier.org

Global Microbial Identifier

Moving on *each meeting approx. 100-400 participants*

”GMI” 1-4, USA & Europe 2011-12	Initiating discussions
GMI 5, Copenhagen, *Feb 2013*	Preparing a Road Map
GMI 6, California, *Sep 2013*	Agreeing a Charter
GMI 7, York UK, *Sep 2014*	Constructing an Organization
GMI 8, Beijing, *May 2015*	Moving on
GMI 9, Rome, May 2016	Including developing countries
GMI 10, Cabo San Luca, May 2017	Strengthening health involvement

Data sharing - in my opinion a public good:

In the future sharing of NGS data will occur, no matter what

The most damage (in relation to health, but also politically) is done when data is concealed as part of a cover-up

Experience shows that (even dangerous) data always gets out

There is so much to gain (in relation to health, food safety, but also to economy) if we share data

NGS leap-frog potential in developing countries:

New diagnostics avoids need for specialized training (testing for Salmonella and Norovirus the same)

New diagnostic systems reaching further

with real-time characterization of microorganisms
in decentralized labs w sequencers + internet

NGS enable uniform lab-based *surveillance systems*

Same-same for humans & animals - **One Health**

Moving forward - together

- Salmonella solutions in Denmark were possible only because researchers, regulators and food industry worked together

- The key driver for this common move was the recognition of the new scientific tool: source attribution, and the agreement to share data to support the efficient use of this tool!

- WGS will not only enable better, faster and more correct determination of a connection between outbreak strains in patients and food, it will also enable source attribution for all microorganisms

Major obstacles

- Researchers Pride:
- Industry’s Reluctance:
- Country’s ‘sovereign right’:

GMI is recognized

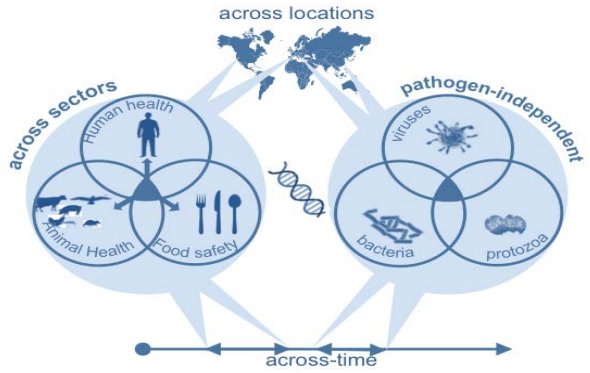
- The fact that NCBI and EBI recognize GMI as a conceptual first step towards global harmonization shows that GMI work is working

- The WHO and FAO are represented in the Steering Committee and intends to initiate a two-year Expert Meeting process to investigate the NGS potential – within a GMI framework!

- OIE (World Organization for Animal Health) has reached out to GMI, recognizing the need for cross- sectoral standardization, now also Member of Steering Committee

Anything happening in Europe?
Compare vision: one system serves all
(EU Horizon2020)

COllaborative **M**anagement **P**latform for detection and **A**nalyses of (**R**e-) emerging and foodborne outbreaks in **E**urope

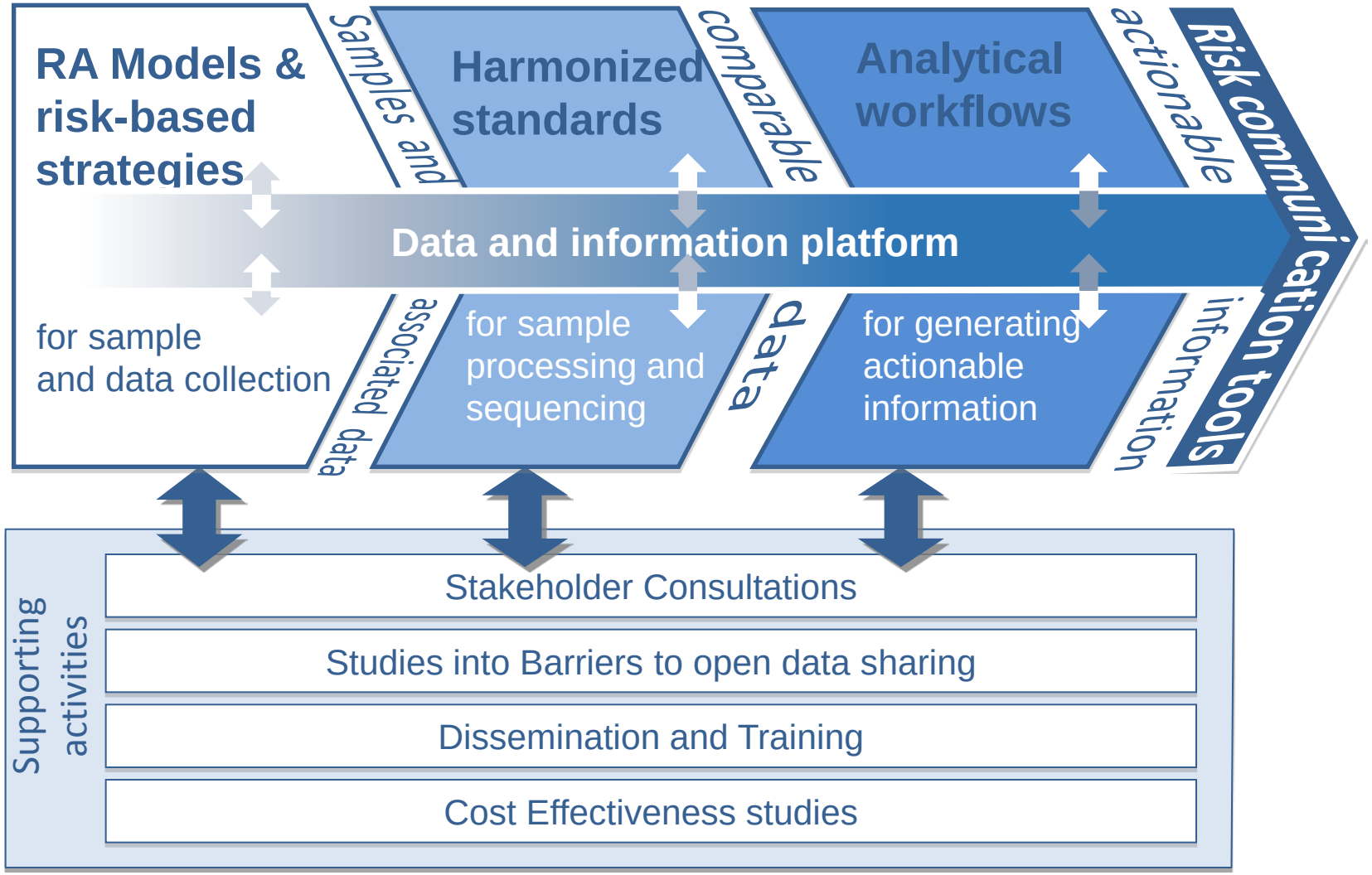


COMPARE as the enabling system for rapid identification, containment and mitigation of emerging infectious diseases and foodborne outbreaks by generation and comparison of genomic information on samples and pathogens across sectors, time and locations, with contextual additional data.

Guiding principles:

- Cross sector
- Cross domain
- Open source
- Interaction with the rest of the World (all inclusive)
- Data for action (actionable outputs)

Project structure



Consortium

Compare

Multidisciplinary expertise in human health, animal health and food safety

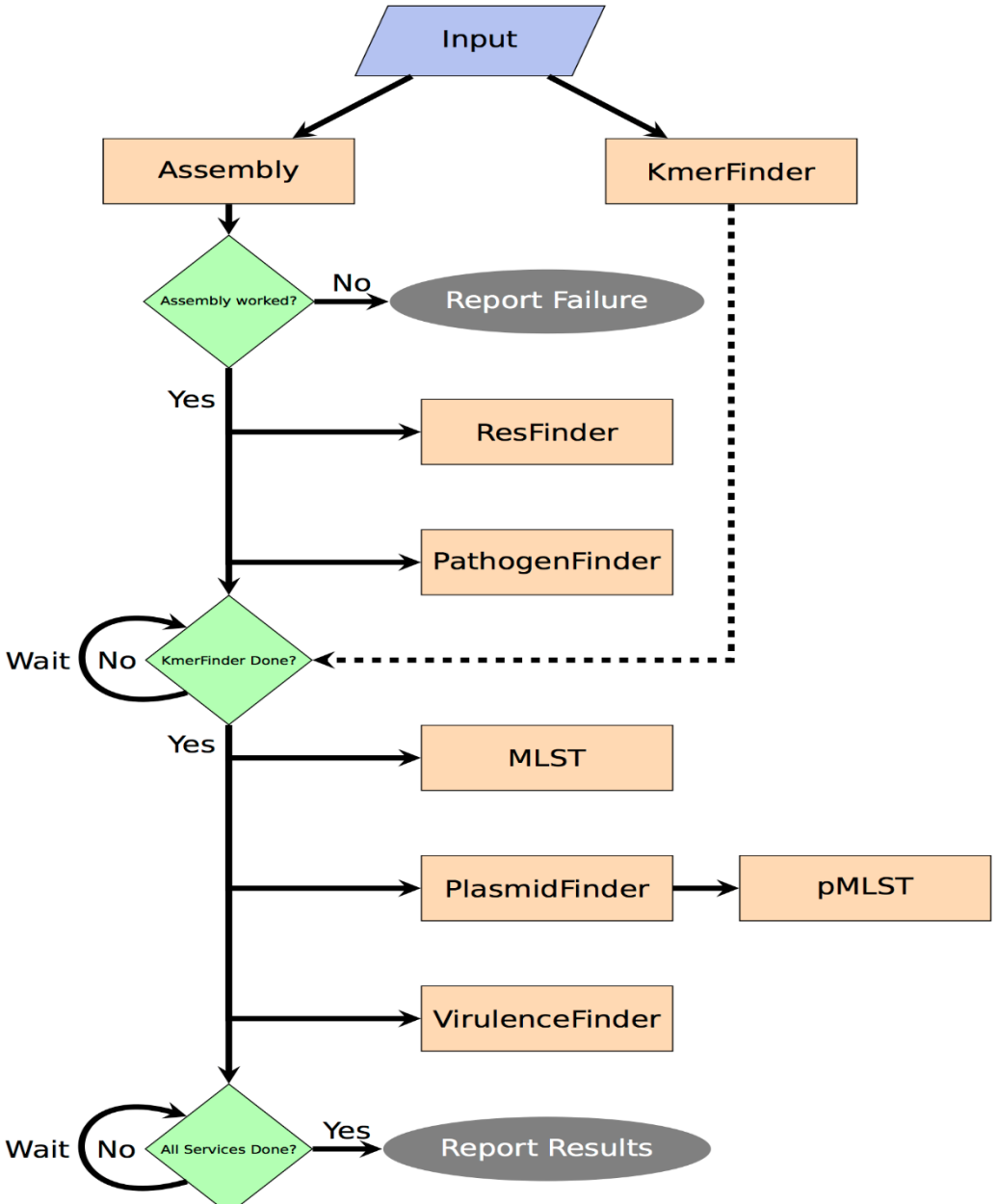
System Architecture &, software , Bioinformatics, computing.

Communication expertise

Health economics, cost effectiveness

DTU's "CGE" analysis workflow
(DTU: Technical University of Denmark)

- Generalist bacterial analysis
- Provides
  - typing (MLST)
  - resistance genes
  - virulence genes
  - SNP- based trees
  - etc.



Starting the inter-governmental discussion

GMI will next week start sending out **a Letter to the Ministries of Health**, cc'ing Ministries of Agriculture to all countries of the world.

The purpose is to convince member states of the need to discuss the global potential of this new technology and to put global WGS implementation on the agenda of relevant inter-governmental Organizations, notably WHO, FAO and OIE.

The debate – and the decisions – of Inter-governmental Organizations, such as WHO, is primarily driven by Member States. Thus the need for Ministers of Health to get this message NOW.

Letter to the Governments:

Suggesting that the global community should embrace the new technical opportunities presented by WGS for Health, Agriculture and Society

by:

- Considering the construction of a global platform and inter-connected WGS databases integrating national and international efforts in a One Health framework

enabling:

- Significant WGS-based improvement of surveillance and outbreak response, sharing information on virulence, supporting new therapies and vaccines

addressing:

- The rise of AMR, a critical challenge identified by the United Nations in a recent (2016) resolution

and supporting:

- The characterization and development of beneficial microorganisms (used in food production or environmental management).

GMI11: Global in Geneva

GMI11 will be hosted by WHO in Geneva the week of 14.05.18 – the week before the World Health Assembly (WHO's Governing Body)

It is hoped that we can use some of the experts participating in GMI11 for side-events to WHA – such side-events can be official part of the programme, or simply be hosted by countries

In a perfect situation the discussion about sharing WGS data and building platforms and databases would also be in the WHA programme, i.e. being discussed with a view of producing a WHA Resolution text, in 2019.

WHA Resolutions outlines the specific directions for WHO and Member States

We have to start showing what can be done

We all agree there is a need to inform/persuade political level in countries (especially developing countries) about the dramatic new potential of NGS

So, why don’t we start small projects enabling both the build-up of NGS capacity and the documentation of potential at national/regional level

NTU-FAO NGS project on food safety management

- Project initiated in response to an articulated need from participants expressed during NTU/FAO/WHO/ INFOSAN Meeting, Nov. 2016, Singapore
- Urgent need to build national capacity for the interpretation of NGS data and create regional NGS database(s);
- Project can be a starting point to generate relevant (NGS) data for foodborne pathogens and antimicrobial resistance (AMR) surveillance in the region
- Sequence data will be analysed by online tools (http://www.genomicepidemiology.org/) created by WHO Coll. Centre (DTU)

We choose to create this system in this decade, not because it is easy, but because it is hard,

because that challenge is one that we are willing to accept, because that challenge will bring so much benefit to global health and global food science and safety

www.globalmicrobialidentifier.org

Global Microbial Identifier