



METHYLENE BLUE-TREATED FRESH FROZEN PLASMA AND RELATED ADVERSE REACTIONS IN FRANCE: THE LONGER THE EXPERIENCE THE MORE ROBUST THE RESULTS

Ignacio Alvarez, Macopharma Clinical Scientific Manager, France
Stefan Reichenberg, Macopharma Scientific Marketing Manager, Germany

ADVERSE REACTIONS IN CONTEXT

- Reporting improvement
- Increasing allergic reactions in the normal population
- Increasing incidence of reactions?

ADVERSE REACTIONS IN CONTEXT

Reporting improvement

From 2006, the number of declarations has increased by an average of **13% per year***

ANSM, the French Agency for Safety of Health Products, received 13,785 declarations in 2011, an increase of **31%** compared to 2010*

**2011 ANSM Haemovigilance Report*

ADVERSE REACTIONS IN CONTEXT

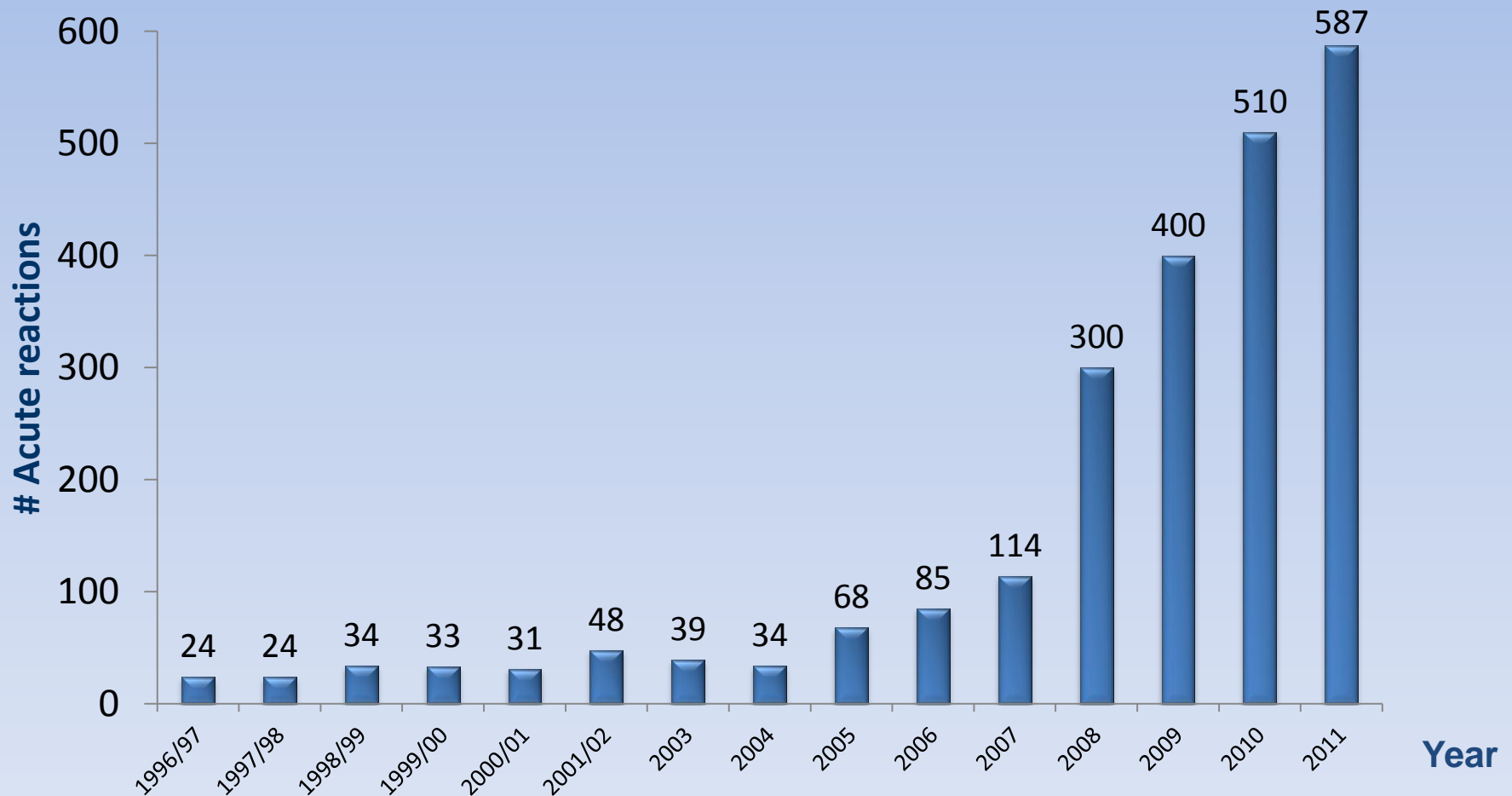
● Increasing allergic reactions in the normal population

A steady increase in the prevalence of allergic diseases globally has occurred with about **30-40%** of the world population now being affected by one or more allergic conditions*

Adverse drug reactions (ADR) may affect up to **1/10** of the world's population and affect up to **20%** of all hospitalized patients. More than **10%** of all ADR are unpredictable drug hypersensitivity reactions*

**World Allergy Organization White Book on Allergy 2011-2012: Executive Summary*

ADVERSE REACTIONS IN UK



Annual SHOT (Serious Hazards of Transfusion) Report 2011

BACKGROUND

In 2011, the French Agency for Safety of Health Products (AFSSAPS, now ANSM) decided to withdraw MB-treated plasma for alleged excessive related allergic reactions based on the 2010 HV report.

The assessment was based on 2005-2010 data.

MB-Plasma implementation from mid-2008 in France.

SEQUENCE OF EVENTS: 2008

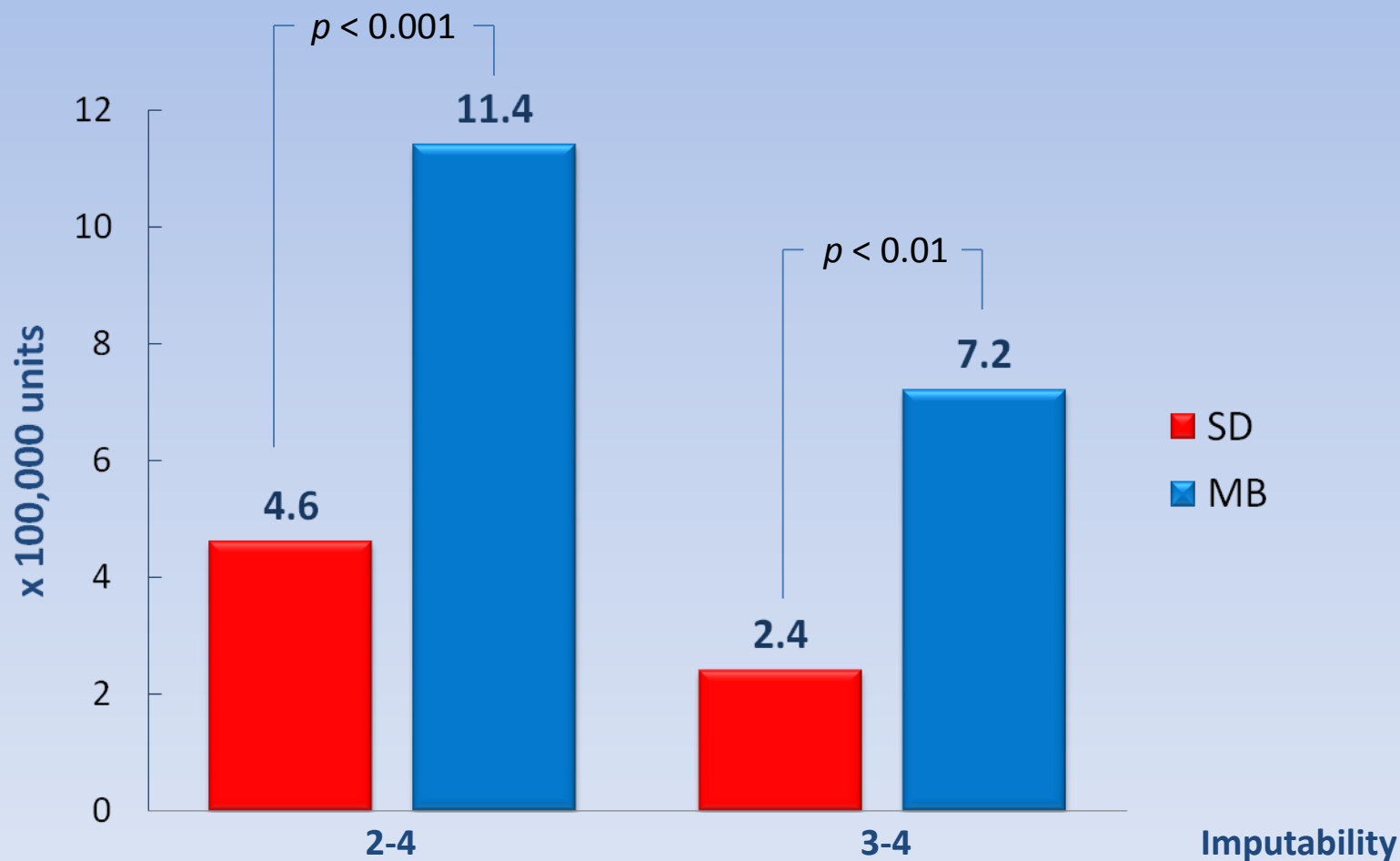
On June 30th 2008, the National Haemovigilance Commission installed a **Working Group (GT Allergie)** to specifically investigate allergic reactions due to blood products.

Starting in September 2008, AFSSAPS observed a **higher than expected frequency** of serious allergic reaction notifications (Grade 2 & 3):

➤ *1/5,900 with MB-Plasma versus 1/19,800 with other FFP**

**2008 AFSSAPS Haemovigilance Report*

SEQUENCE OF EVENTS: 2009*



*2009 AFSSAPS Haemovigilance Report – (Severity 2-3)

SEVERITY GRADE CLASSIFICATION*

| Previous severity grade of immediate allergic reactions | New severity grade of immediate allergic reactions |
|--|--|
| Grade 1 (Minimal reactions) | Grade 1 (Minimal reactions) |
| Grade 2 (Reactions with physiological effects) | Grade 2 (Moderate reactions) |
| Grade 3 (Reactions with average or severe physiological effects) | Grade 3 (Severe reactions) |
| Grade 4 (Fatal reaction) | Grade 4 (Fatal reaction) |

**2010 AFSSAPS Haemovigilance Report*

SEVERITY CLASSIFICATION UPDATE*

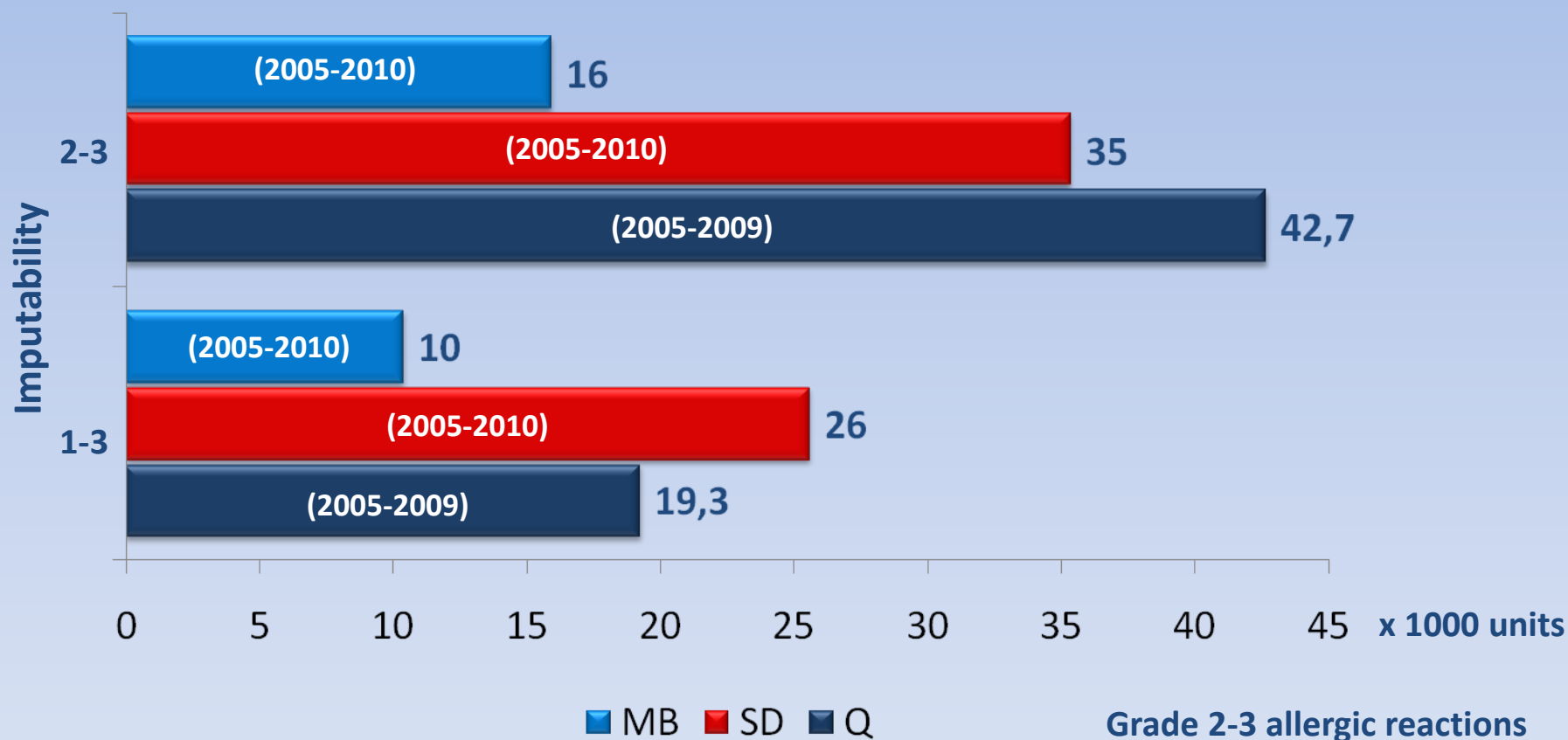
Severity grade of immediate allergic reactions

| Grade and Previous Definition | | e-FIT Grade and New Definition | |
|--------------------------------------|---|---------------------------------------|---|
| 1 | Generalized cutaneous-mucosal signs | 1 | Generalized cutaneous-mucosal signs: Erythema, urticaria, angio-oedema |
| 2 | At least 2 organs involved | 1-3 | At least 2 organs involved : cutaneous-mucosal signs, CV symptoms (moderate hypotension), respiratory symptoms (any, dyspnoea, bronchospasm), digestive symptoms. |
| 3 | CV collapse (shock, tachycardia or bradycardia, arrhythmia). ± grade I–II symptoms | 3 | CV collapse (shock, tachycardia or bradycardia, arrhythmia). ± grade I–II symptoms. |
| 4 | CV or respiratory arrest. Death | 3 | Cardiac or respiratory arrest. 4 with death (ineffective reanimation) |

IMPUTABILITY CLASSIFICATION UPDATE*

| Imputability classification of adverse events | | | |
|---|----------|-----------------------|-----------|
| Previous Definition | Grade | New Definition | Grade |
| Excluded | 0 | Not evaluable | NE |
| Doubtful | 1 | Excluded / Improbable | 0 |
| Possible | 2 | Possible | 1 |
| Probable | 3 | Probable | 2 |
| Certain | 4 | Certain | 3 |

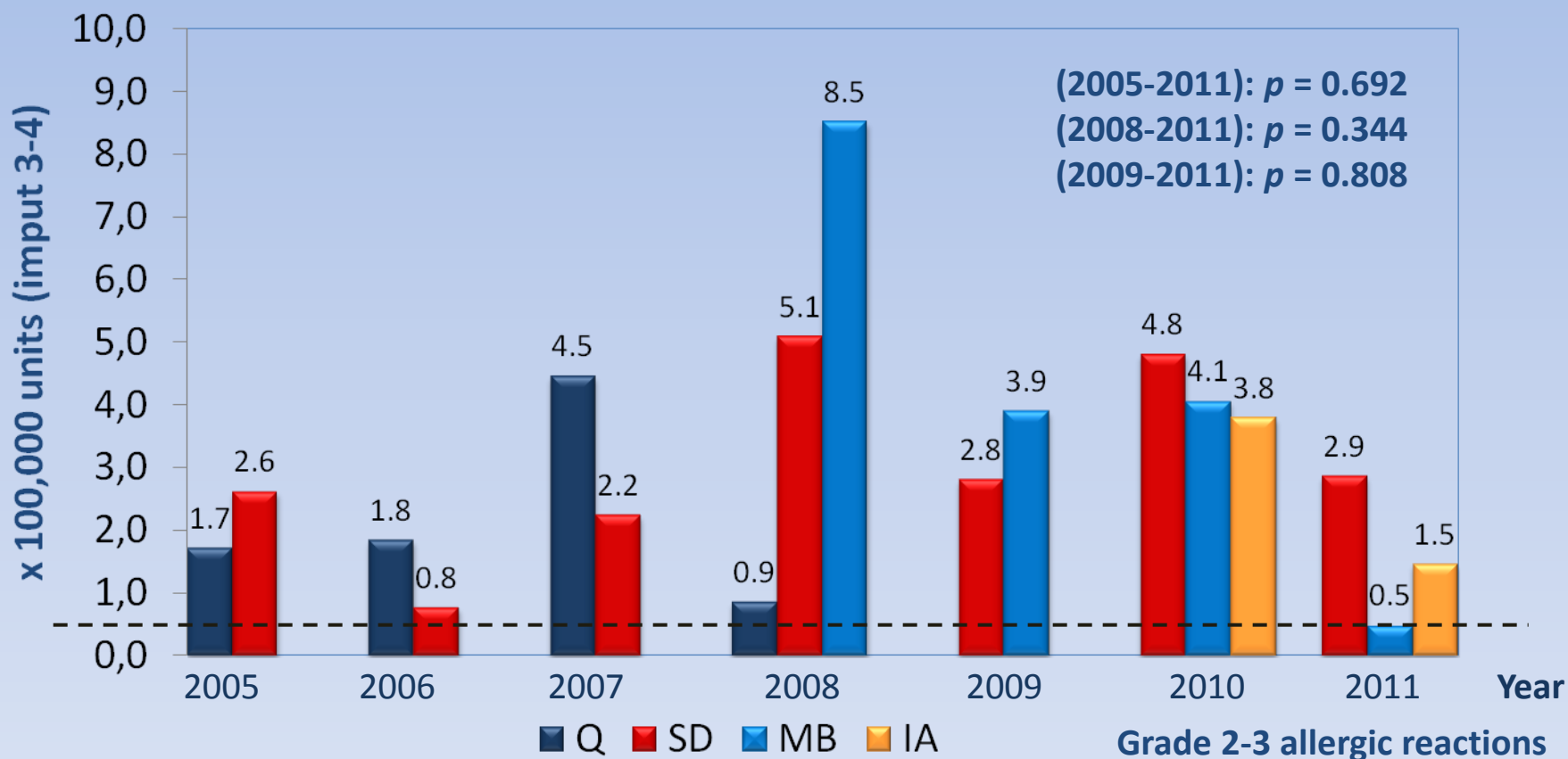
SEQUENCE OF EVENTS: 2010*



*2010 AFSSAPS Haemovigilance Report

Reminder: MB-Plasma implementation from mid-2008 in France

EVOLUTION OF AR PER YEAR*



*2005-2011 AFSSAPS/ANSM Haemovigilance Reports

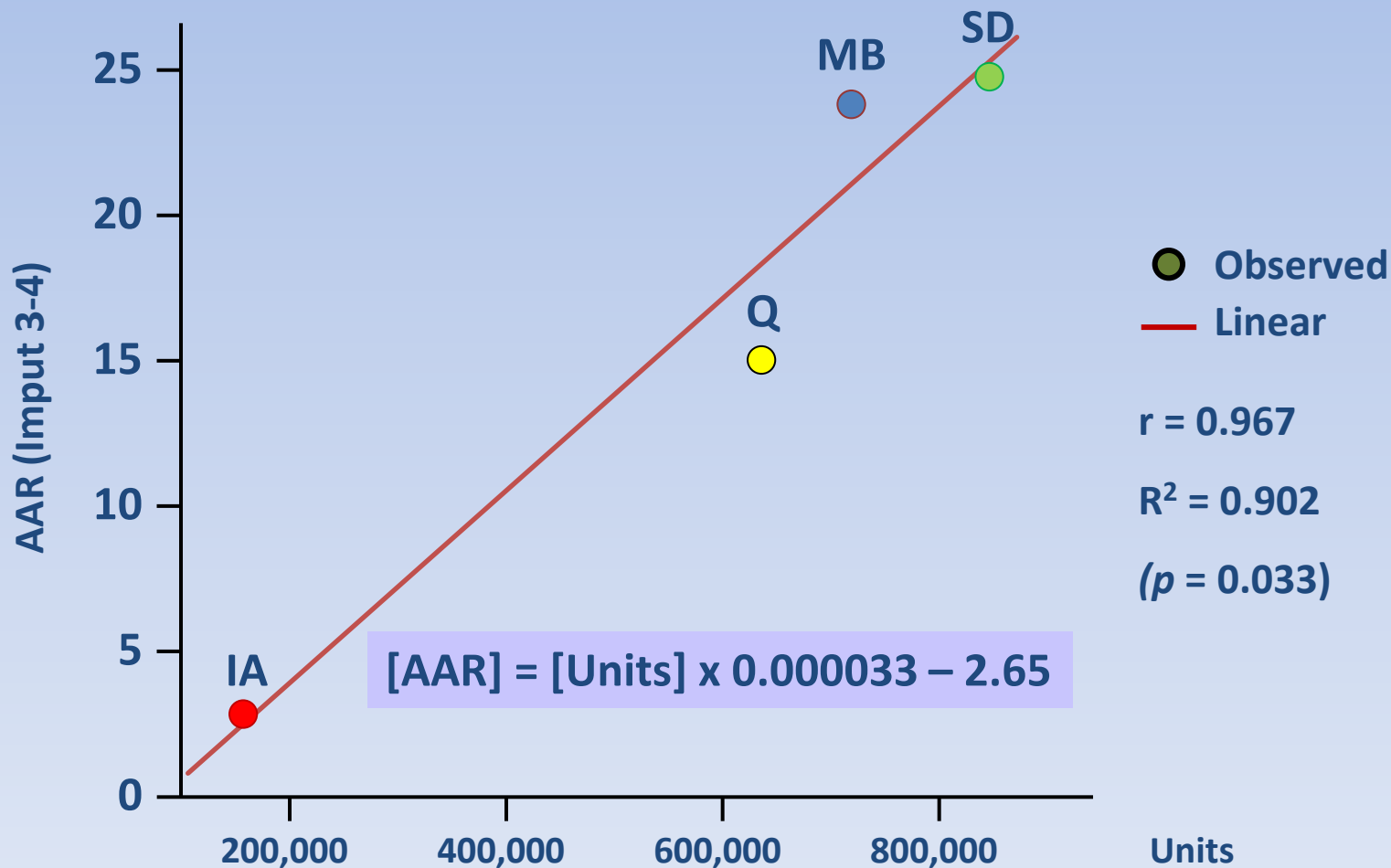
INCIDENCE DEFINITION

Number of new cases of adverse events in given time period / total number in population at risk at that time period

- **The time period should be specified, as the number of incident cases can be made arbitrarily large or small depending on the length of the time period being considered.**
- **‘At Risk’ population. People treated during the time period are included in the denominator – if they are not exposed to the treatment, they are not at risk of developing adverse events.**

REGRESSION ANALYSIS

(2005-2011)



CONCLUSIONS

No significant differences were observed in the incidence of moderate/severe allergic reactions among the different fresh frozen plasmas, used in France between 2005 and 2011, with or without pathogen reduction system.

A significant increasing linear correlation between the number of allergic reactions and the number of units transfused with the different FFP was found.

**“IF YOU TORTURE THE DATA LONG ENOUGH
THEY WILL EVENTUALLY CONFESS”**

Prof. Ronald Harry Coase

Nobel Memorial Prize in Economics, 1991