RAPID OUTBREAK ASSESSMENT

Unusual increase of *Salmonella* Mikawasima infections in humans

28 November 2013

Summary

An unusual increase in the number of *S.* Mikawasima infections in humans has been observed in several EU countries since September 2013, and a gradual increase in the reported number of infections has been observed since 2009 in the EU/EEA as a whole.

Epidemiological and microbiological investigations do not allow conclusions to be drawn on whether the cases are linked. Considering that *S.* Mikawasima is an uncommon serovar the concomitant increase in number of cases in several countries, although seasonally typical for this serovar, suggests a common exposure. Additional microbiological investigation, through whole genome sequencing should provide further microbiological evidence in support of a common source of infection. Further epidemiological investigations are on-going and are expected to provide more information for the assessment of risk to EU citizens.

The *S.* Mikawasima isolates recorded in animals should be assessed in view of the recent increase in the number of human cases. This may support the generation of epidemiological hypothesises for testing, with the aim of identifying a common source of transmission.

In the light of evidence from the European Surveillance System (TESSy) data and the European Food Safety Authority (EFSA) database of an increase in human cases, and detection of this *Salmonella* serotype in animal, food and feed, a multi-sectorial investigation is recommended to understand and assess the risk associated with this increasing trend of *S.* Mikawasima infections in the EU/EEA.

ECDC is monitoring the situation through the Epidemic Intelligence Information System for Food- and Waterborne Disease and Zoonoses (EPIS-FWD) and will update this assessment as new information becomes available.

Public health issue

Unusual increase of *Salmonella* Mikawasima infections in humans in the EU/EEA

Source and date of request

ECDC internal decision, 18 November 2013

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ECDC acknowledges the valuable contributions from the above-mentioned experts and institutions. All experts have completed a Declaration of Interest. Opinions expressed by individual experts do not necessarily represent the opinion of their institutions.

Disease background information

S. Mikawasima literature review

Salmonella enterica serovar Mikawasima (*S.* Mikawasima) is an uncommon serovar in the EU/EEA.

Salmonella Mikawasima was first isolated from tortoises in Turkey in 1967 [1]. The first report of *S.* Mikawasima isolation in the EU/EEA dates back to 1976, in the context of a large study on *Salmonella* prevalence in pigs in the Netherlands [2].

Most of *S.* Mikawasima reports are localised in Spain. In particular, a study conducted in 1999 reported *S.* Mikawasima to be the predominant serovar detected in environmental samples (fresh waters) in north-east Spain [3]. More recently, in 2011–2012, *S.* Mikawasima was also isolated from pigs and wild boars in southern and northern Spain [4,5].

In the years 1993–2000 *S.* Mikawasima was isolated repeatedly in hospital settings in several regions of Spain [6], including resistant strains, the last report of which is from this year [7,8]. Extended-spectrum (beta)-lactamase-producing *S.* Mikawasima was also detected in Germany in 2009 [9]. A recent retrospective study from the Czech Republic reports several sporadic cases of *S.* Mikawasima in six regions of the country in 2012 [10].

In the EU/EEA, one outbreak of *S.* Mikawasima causing human gastroenteritis has been published. A cluster of nine cases was identified in October 1992 in the South West Thames region in the UK. Epidemiological investigations identified doner kebabs as a probable source [11].

A search in the Rapid Alert System for Food and Feed (RASFF) database resulted in one notification posted in 2005 related to *S.* Mikawasima presence in frozen squid tentacles from India.

A search of the Epidemic Intelligence Information System for Food- and Waterborne Disease and Zoonoses (EPIS-FWD), resulted in two Urgent Inquiries (UI) about *S.* Mikawasima. The first one, posted by Finland in March 2008, reported a possible cluster of cases. A more recent one was posted by Denmark in October 2012 reporting a possible outbreak. Among the countries that replied to the UI, Norway reported a marked increase in the number of cases as well.

Additional information on *Salmonella* infection in humans may be found at:
http://ecdc.europa.eu/EN/HEALTHTOPICS/SALMONELLOSIS/Pages/index.aspx

Epidemiological overview of *Salmonella* Mikawasima in EU/EEA

From 2007 to 2012, 671 human cases of *S.* Mikawasima cases were reported from EU and EEA countries to the European Surveillance System (TESSy). There has been a steady increase in the number of cases since 2009 (Figure 1). Analysis of the *S.* Mikawasima cases reported for quarter one and two of 2013 showed a significant peak in May (11 cases) as compared to historical average of the same month (3.6 cases). This peak is largely due to cases reported by the UK (9/11 cases). The annual proportion of domestic cases has remained constant at 80% or more, suggesting that *S.* Mikawasima is an endemic but rare serovar in the EU/EEA.

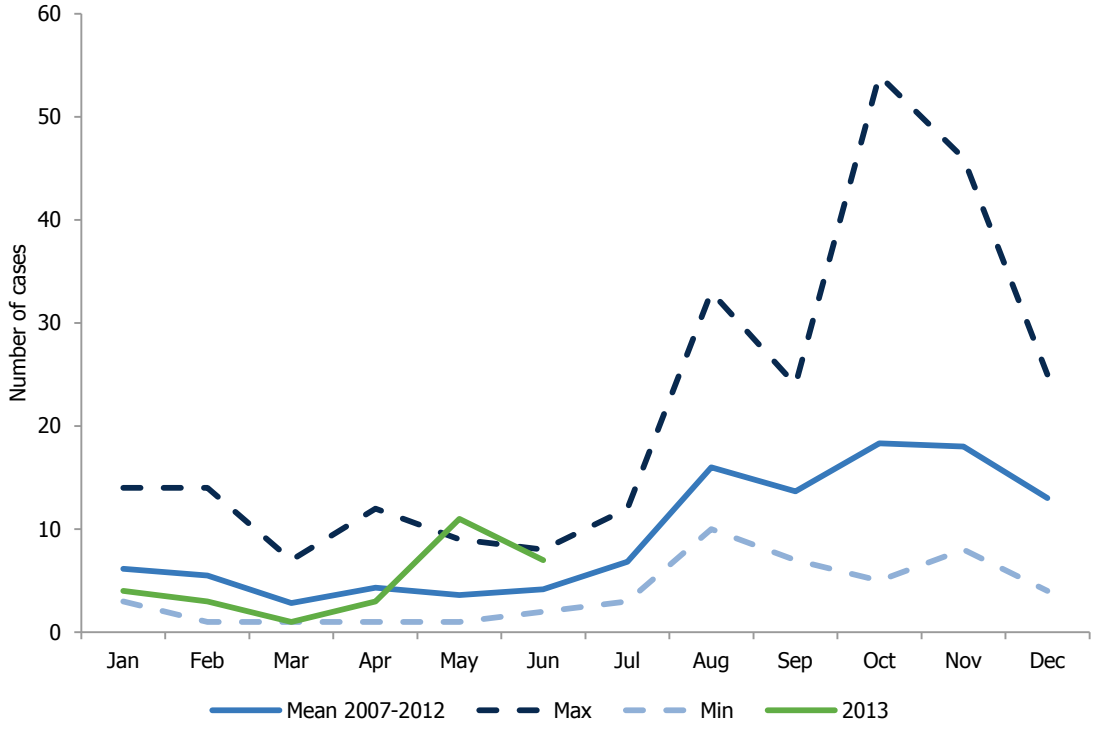
Figure 1. Distribution of confirmed cases of *S.* Mikawasima by year of reporting, in EU/EEA, 2007-2012 (N=671).

Source: TESSy, countries reporting at least one case during the period: Austria, Belgium, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Italy, the Netherlands, Norway, Sweden, the United Kingdom

The case distribution shows a marked seasonality over months, with regular peaks in the period September-November. This seasonality is largely driven by the reporting of domestic cases while reporting of travel-related cases shows little fluctuation in this period.

Based on TESSy historical data from 2007 to 2012 for the reporting EU/EEA countries, 18 cases of *S.* Mikawasima were reported on average per month in October and November. According to the seasonal distribution observed during 2007–2012 (Figure 2), the maximum number of cases observed per month in historical data was 54 cases.

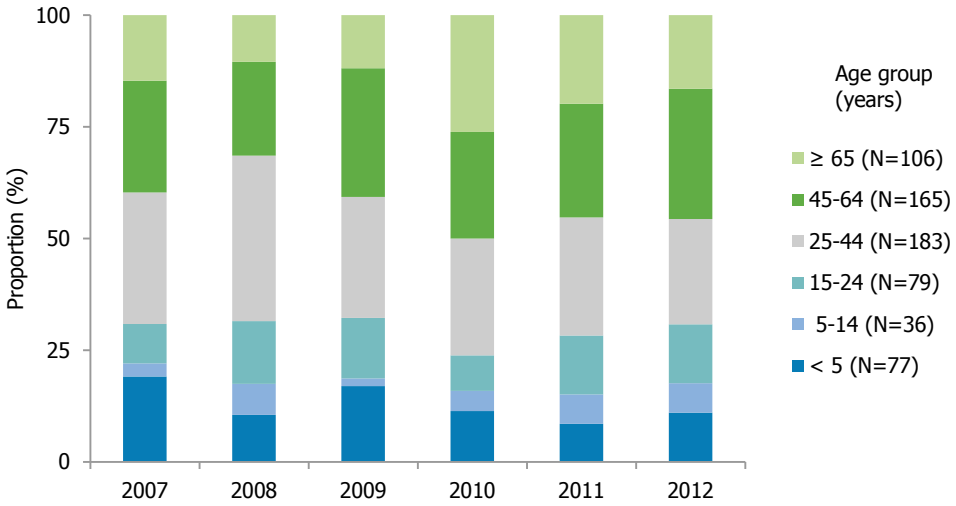
Figure 2. Distribution of average, maximum and minimum for 2007–2012 compared with 2013 reported *S.* Mikawasima cases by month, in the EU/EEA, 2007–2012



Source: TESSy, countries reporting at least one case during the period: Austria, Belgium, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Italy, the Netherlands, Norway, Sweden, the United Kingdom

No significant difference was detected between genders across years and the male-to-female ratio was rather constant; 0.88:1 over the years 2007–2012. The majority of cases were among adults, with ≥ 65% of the cases reported in the age groups over 25 years in 2007–2012 (Figure 3).

Figure 3. Proportion of *S.* Mikawasima cases by age group and year in EU/EEA, 2007–2012 (N=646)



Source: TESSy, countries reporting at least one case during the period: Austria, Belgium, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Italy, the Netherlands, Norway, Sweden, the United Kingdom

No death was reported and there is no indication that the clinical presentation of these cases differs from usual *Salmonella enterica* infections, especially in terms of severity.

Salmonella Mikawasima in animal, food and feed

The annual reporting of zoonoses in accordance with Directive 2003/99/EC* provides an opportunity for Member States and the other reporting European countries to report data on *Salmonella* serovars isolated from food, feed and animal samples. Not all Member States systematically report serotyping results of *Salmonella* isolates and the reporting does not always cover all available food and animal sources. Data are mostly reported at the *Salmonella* genus level, as provision of the surveillance and control of *Salmonella* in food and animal respectively concerns *Salmonella* spp. or certain serovars of public health significance (such as *S.* Enteritidis and *S.* Typhimurium), to which *S.* Mikawasima do not belong. Nevertheless, substantial amounts of data are available from this reporting over the years, and the data suggest that *S.* Mikawasima is a rare serovar (table 1).

During 2004—2012 (including some data from 2013), 120 isolates of this serovar were reported from food, feed and animals. These reports come from eight Member States and one Non-Member State. Most of the isolations were reported from animals, particularly from *Gallus gallus* (fowl) and pigs. However, the higher number from *Gallus gallus* may only be due to the mandatory *Salmonella* control programmes in this animal species, which regularly provide isolates for typing. There were also some mostly single isolations from various food sources, such as vegetables, sausages meat and nuts. In addition, some isolations were made from feed, mainly from pet food. There are more isolations of *S.* Mikawasima from 2010 than from previous years.

* Directive 2003/99/EC Of The European Parliament And Of The Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF

Table 1. Isolations of *S.* Mikawasima from annual reporting on zoonoses in accordance with Directive 2003/99/EC in 2004–2013, from the EU-wide baseline surveys and from additional data provided by some EU Member States

Source	No. of isolations in 2004—2009	No. of isolations in 2010—2011	No. of isolations in 2012–2013*	Total no. of isolations in 2004-2013*
Animals, in total	**36**	**44**	**11**	**91**
Gallus gallus (fowl), in general	12	26		38
Broilers	1	7	10	18
Laying hens	3	7	1	11
Pigs	10	3		13
Ducks	2	1		3
Poultry, in general	2			2
Cattle	4			4
Domestic solipeds	2			2
Food, in total	**10**	**7**	**4**	**21**
Food of non-animal origin *(unspecified category)*	5			5
Vegetables	1	4 (tomatoes)		5
Fruit	1			1
Sweets	1			1
Sausages	2			2
Bovine meat				1
Rice salad		1		1
Frock legs		1		1
Broiler meat		1	2	2
Wild boar meat			1	1
Almonds			1	1
Feed	**1**	**6**	**1**	**8**
Totals	**47**	**57**	**16**	**120**

Source: EFSA's database
**Data from 2013 are not comprehensive, and includes only available data at the 26 November 2013*

Event background information

Description of the current event on unusual increase of *Salmonella* Mikawasima in the EU

On the 8 November 2013, through the EPIS-FWD platform, the UK reported an unusual increase in laboratory reports of domestic cases of *S.* Mikawasima from September to November 2013. Fourteen Members States have replied to the urgent inquiry in EPIS-FWD. Five countries, Denmark, France, Germany, Spain and Sweden, reported temporally linked domestic cases. Of these, Denmark, Sweden and Germany also reported an associated increase above the national average for the period (Table 2).

Italy, Ireland, Norway, Finland, Greece, and Austria reported one to three cases each since January 2013, in line with the national average for the year.

Molecular investigations in the UK have revealed the co-existence of two *S.* Mikawasima Pulsed Field Gel Electrophoresis (PFGE) -*Xba*I profiles, each with their own geographical distribution: Profile A and profile B. PFGE-typing of the strains in Denmark revealed an indistinguishable profile to the profile A identified in the UK. Further PFGE-typing is currently on-going in the UK, Denmark, France and Sweden; and whole genome sequencing is being performed in Denmark and the UK for further comparison.

Table 2. Confirmed cases of *S.* Mikawasima as reported by Member States in EPIS FWD, September-November 2013 (as of 28 November 2013)

Country	No of cases (September—November 2013)	Unusual increase at the national level	Molecular investigation (PFGE analyses)
United Kingdom	75	Yes	Outbreak profile A and B
Denmark	11	Yes	Outbreak profile A
Germany	9	Yes	Not available
Sweden	6	Yes	On-going
France	7	No	On-going
Spain	9	No	Not available
Total	117		

Country specific information

United Kingdom: Seventy-five domestic cases were reported by the UK. Of these, 29 were clustered in Scotland and 46 clustered in England, Wales and Northern Ireland. Thirty-nine cases are female (52%) and 36 are male. The median age is 43 years (range 1–85).

Denmark: Eleven domestic cases were reported. The date of onset for the cases was between 9 and 22 October 2013. The median age was 28 years, ranging from 3 to 100 years, and an even gender distribution. For eight cases, PFGE profile was available and identical to PFGE profile A. Six cases were interviewed using trawling questionnaires.

Sweden: Six domestic cases were reported with a date of onset of between 23 October and 2 November 2013. The median age was 69 years, ranging from 13 to 89 years, and an even gender distribution. PFGE analysis is on-going.

France: Seven domestic cases were reported with a date of onset between 13 September and 18 October. The median age was 65 years, ranging from 21 to 94 and an even gender distribution. PFGE analysis is on-going. Interviews are planned.

Germany: Nine domestic cases were reported with date of onset between 8 October and 6 November 2013. The median age was 33 years, ranging from 17 to 89 years, and an even gender distribution. No PFGE profile is available.

Spain: Nine domestic cases were received in the NRL from the beginning of September to the middle of November. The median age was 49 years, ranging from <1 year to 82 years. Six were female and three male. No PFGE is available. Interviews are planned.

Results of the microbiological investigations

S. Mikawasima genetic diversity in the EU/EEA: historical perspective based on PulseNet Europe database

Twenty-six PFGE-*Xba*I isolates of *S*. Mikawasima are present in the historical PulseNet Europe database, which includes 21 748 PFGE entries covering the years 1994–2012. PFGE patterns of *S*. Mikawasima show a limited diversity with 22 (85%) isolates distributed in only two major clusters. Among these 22 isolates, seven isolates share indistinguishable PFGE-*Xba*I pattern with the *Xba*I profile reported in the UK (profile A); four are from Finland, isolated in 2008 (three) and 2009 (one), one from the UK isolated in Scotland in 2007, one from Denmark isolated during an outbreak in 2012, and one from Ireland undated.

PFGE analysis of isolates of *S*. Mikawasima submitted to the TESSy production database

As of 18 November, 42 isolates of *S*. Mikawasima were included in the pilot TESSy database. PFGE analysis of these isolates show two major clusters covering almost 75% of isolates. The largest cluster is composed of 23 (55%) isolates and shares an undistinguishable PFGE-*Xba*I pattern (*Xba*I type 0063) with the first PFGE-*Xba*I profile reported by the UK (profile A). This cluster includes isolates from Denmark (six, 2012–2013), Spain (one, 2013), Ireland (one, 2009) and UK (15, 2012–2013). The second cluster comprises of eight isolates obtained in 2011 and 2012 in Ireland (three) and UK (five), all belonging to the *Xba*I type 0060. After a preliminary analysis, this *Xba*I pattern shows a close relatedness with the second PFGE profile reported by the UK (profile B).

ECDC threat assessment for the EU

From 27 September to 1 November 2013, the UK observed an increase in the number of *S*. Mikawasima domestic cases with 75 laboratory reports. As of 26 November 2013, five other EU Member States have reported an additional 42 cases. No cases have been reported in the UK or Denmark since 1 November. However, since other countries reported more recent cases, the outbreak may be considered as on-going.

The analysis of TESSy data showed an upward trend of *S*. Mikawasima cases in the EU/EEA since 2009, with the large majority of cases reported by the UK and Spain. Based on TESSy historical data, the number of cases observed so far in October and November 2013 in the EU/EEA is above expectations.

PFGE-typing of a subset of human isolates from UK and Denmark yielded indistinguishable PFGE profiles, suggesting a potential link between the cases. However, the low discriminatory power of PFGE typing does not allow firm conclusions to be drawn. Additional molecular analysis, including whole genome sequencing, should provide further evidence.

Epidemiological background data, along with the molecular typing findings, suggest at least one source of *S*. Mikawasima infection that may be common to some or all of the EU countries reporting an increase in human cases.

The UK and Denmark have been interviewing cases with trawling questionnaires. The UK will conduct a case control study, with the support of ECDC, inviting all affected countries to participate.

The *S*. Mikawasima isolations in animal, food and feed reported by EFSA in 2010—2013 does not provide sufficient evidence of a possible common source of infection due to the marked diversity of the animal populations and food categories from which *S*. Mikawasima has been isolated, and the scarcity of the isolations.

Conclusions and recommendations

An unusual increase in the number of *S.* Mikawasima infections in humans has been observed in several EU countries since September 2013, and a gradual increase in the reported number of infections has been observed since 2009 in the EU/EEA as a whole.

The current epidemiological and microbiological investigations do not allow conclusions to be drawn on whether the cases are linked. Considering that *S.* Mikawasima is an uncommon serovar, the concomitant increase in number of cases in several countries, although seasonally typical for this serovar, suggests a common exposure. Additional microbiological investigation, through whole genome sequencing, should provide further microbiological evidence in support of a common source of infection. Further epidemiological investigations are on-going and are expected to provide more information for assessment of risk to EU citizens.

The *S.* Mikawasima isolates recorded in animals should be assessed in view of the recent increase in the number of human cases. This may support the generation of epidemiological hypothesises for testing, with the aim of identifying a common source of transmission.

In the light of the evidence from TESSy data and the EFSA database of an increase in human cases, and detection of this *Salmonella* serotype in animal, food and feed, a multi-sectorial investigation is recommended to understand and assess the risk associated with this increasing trend of *S.* Mikawasima infections in the EU/EEA.

ECDC is monitoring the situation through EPIS FWD and will update this assessment as new information becomes available.

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