days 3 and 14 p.i. Sero-conversion to H5 influenza virus was not detected in any birds, indicating that the chickens were not infected with R(Dk/Mong-Dk/Mong). In the histopathological examination, influenza virus antigens were detected in the brain, liver, spleen, kidneys, heart, lungs, pancreas, and colon of chickens inoculated either with Ck/Yamaguchi/04 or with Dk/Yokohama/03. Since severe virus encephalitis with perivascular infiltration in the brain affected one chicken inoculated with Dk/Yokohama/03 (Fig. 1A) and higher titers were detected in the brains of chickens inoculated with Dk/Yokohama/03 than with Ck/Yamaguchi/04, it was found that infection with Dk/Yokohama/03 caused severer lesions than infection with Ck/Yamaguchi/04 in the brain.

Quails

All of the quails inoculated with Ck/Yamaguchi/04 and Dk/Yokohama/03 died between day 2 p.i. and day 3 p.i. (2–3d) and between day 3 p.i. and day 4 p.i. (3–4d), respectively, and virus was recovered from each of the tissues tested (Table 2). Disease signs characterized by severe nervous disorders were observed in 2 out of 6 quails infected with Dk/Yokohama/03. Higher titers of viruses were detected in all the tissues of quails inoculated with Ck/Yamaguchi/04 compared to those inoculated with Dk/Yokohama/03. None of the quails inoculated with R(Dk/Mong-Dk/Mong) had died by day 14 p.i., and virus was not recovered from any of the tissues at day 3 and 14 p.i. Sero-conversion to H5 influenza virus was detected in the quails inoculated with R(Dk/Mong-Dk/Mong) at day 14 p.i., indicating that these quails were infected with R(Dk/Mong-Dk/Mong). In the histopathological examination, in the brain of the quail inoculated with Dk/Yokohama/03, severe virus encephalitis with laminar encephalomalacia (necrosis) was observed (Fig. 1B). Antigens to influenza viruses were detected in the brains and hearts of birds infected either with Ck/Yamaguchi/04 or with Dk/Yokohama/03.

Budgerigars

All of the budgerigars inoculated either with Ck/Yamaguchi/04 or with Dk/Yokohama/03 died by day 5 p.i., and the virus was recovered from each of the tissues tested (Table 3). Disease signs such as severe nervous disorders were observed in 3 out of 7 budgerigars infected with Dk/Yokohama/03. None of the budgerigars inoculated with R(Dk/Mong-Dk/Mong) had died by day 14 p.i., and virus was not recovered from any of the tissues at days 3 and 14 p.i. Sero-conversion to H5 influenza virus was not detected in any budgerigars inoculated with R(Dk/Mong-Dk/Mong) at day 14 p.i., indicating that the budgerigars were not infected with R(Dk/Mong-Dk/Mong).

Ducklings

Two of the ducklings inoculated with Ck/Yamaguchi/04 died on day 6 p.i. and day 7 p.i. (6–7d), and virus was recovered from each of the tissues including

Table 2. Virus recovery and antibody response from quails inoculated with avian influenza virus

Inoculated virus	No. of animals	Days p.i.		Virus recovery[a]						Antibody response[b]
				Respiratory organs	Liver	Kidneys	Colon	Brain	Blood	
Ck/Yamaguchi/04 (H5N1)	7	2–3d	dead	7 (7.4)	7 (7.1)	7 (8.8)	7 (7.2)	7 (8.4)	ND[c]	ND
Dk/Yokohama/03	4	3–4d	dead	4 (6.8)	4 (4.4)	2 (5.7)	3 (6.4)	4 (8.3)	ND	ND
(H5N1)	2	3d	sacrificed	1 (7.2)	2 (6.0)	2 (8.0)	0	1 (5.8)	1 (3.8)	−
R(Dk/Mong-Dk/Mong)	3	3d	sacrificed	0	0	0	0	0	0	−
(H5N1)	2	14d	sacrificed	0	0	0	0	0	0	+

[a]Digit: number of animals in which each virus was isolated. Parenthesis: average of virus titers ($logEID_{50}/g$). 0 indicates no virus was isolated from animals

[b]Antibody detection was examined by ELISA. −: ELISA titer was below 40. +: ELISA titer was over 40

[c]Not determined

Table 3. Virus recovery and antibody response from budgerigars inoculated with avian influenza virus

Inoculated virus	No. of animals	Days p.i.		Virus recovery[a]					Antibody response[b]
				Respiratory organs	Liver	Kidneys	Colon	Brain	
Ck/Yamaguchi/04 (H5N1)	7	3–4d	dead	7 (6.6)	7 (4.3)	7 (7.1)	3 (3.8)	7 (7.4)	ND[c]
Dk/Yokohama/03 (H5N1)	4	3d	sacrificed	4 (5.0)	3 (3.5)	4 (5.4)	4 (2.9)	4 (6.2)	ND
	3	5d	dead	3 (5.3)	3 (2.6)	3 (4.9)	2 (2.9)	3 (8.0)	ND
R(Dk/Mong-Dk/Mong) (H5N1)	3	3d	sacrificed	0	0	0	0	0	ND
	3	14d	sacrificed	0	0	0	0	0	–

[a]Digit: number of animals in which each virus was isolated. Parenthesis: average of virus titers ($logEID_{50}/g$). 0 indicates no virus was isolated from animals

[b]Antibody detection was examined by ELISA. –: ELISA titer was below 40

[c]Not determined

Table 4. Virus recovery and antibody response from ducklings inoculated with avian influenza virus

Inoculated virus	No. of animals	Days p.i.		Virus recovery[a]					Antibody response[b]
				Respiratory organs	Liver	Kidneys	Colon	Brain	
Ck/Yamaguchi/04 (H5N1)	3	3d	sacrificed	3 (5.8)	3 (5.3)	3 (5.2)	3 (3.0)	0	–
	2	6–7d	dead	2 (3.9)	1 (5.5)	1 (5.7)	1 (2.5)	1 (5.3)	ND[c]
	1	14d	sacrificed	0	0	0	0	0	+
Dk/Yokohama/03 (H5N1)	6	3–4d	dead	6 (7.1)	6 (7.1)	6 (5.7)	6 (4.7)	6 (8.1)	ND
R(Dk/Mong-Dk/Mong) (H5N1)	3	3d	sacrificed	0	0	0	0	0	–
	3	14d	sacrificed	0	0	0	0	0	+

[a]Digit: number of animals in which each virus was isolated. Parenthesis: average of virus titers ($logEID_{50}/g$). 0 indicates no virus was isolated from animals

[b]Antibody detection was examined by ELISA. –: ELISA titer was below 40. +: ELISA titer was over 40

[c]Not determined

the brain (Table 4). One of the ducklings survived for 14 days, and from this duckling, specific serum antibodies against H5 influenza virus were detected. All of the ducklings inoculated with Dk/Yokohama/03 died between day 3 p.i. and day 4 p.i. (3–4d), and the virus was recovered from each tissue. None of the ducklings inoculated with R(Dk/Mong-Dk/Mong) had died by day 14 p.i., and virus was not recovered from any of the tissues at days 3 and 14 p.i. Seroconversion to H5 influenza virus was detected in the ducklings inoculated with R(Dk/Mong-Dk/Mong) at day 14 p.i.

Table 5. Virus recovery and antibody response from mice inoculated with avian influenza virus

Inoculated virus	No. of animals	Days p.i.		Virus recovery[a]					Antibody response[b]
				Respiratory organs	Liver	Spleen	Kidneys	Brain	
Ck/Yamaguchi/04	2	3–4d	dead	2 (6.3)	0	1 (3.3)	1 (2.3)	0	ND[c]
(H5N1)	2	3d	sacrificed	2 (6.7)	0	0	0	0	–
	4	14d	sacrificed	0	0	0	0	0	+
Dk/Yokohama/03	4	3d	sacrificed	3 (4.5)	0	0	0	0	–
(H5N1)	4	14d	sacrificed	0	0	0	0	0	+
R(Dk/Mong-	3	3d	sacrificed	3 (4.5)	0	0	0	0	ND
Dk/Mong) (H5N1)	3	14d	sacrificed	0	0	0	0	0	ND

[a]Digit: number of animals in which each virus was isolated. Parenthesis: average of virus titers ($logEID_{50}/g$). 0 indicates no virus was isolated from animals

[b]Antibody detection was examined by ELISA. –: ELISA titer was below 40. +: ELISA titer was over 40

[c]Not determined

Mice

Two of the mice inoculated with Ck/Yamaguchi/04 died on day 3 p.i. and day 4 p.i. (3–4d) (Table 5). Virus was recovered only from the respiratory organs in all except one mouse, which was dead at day 4 p.i. In this mouse, the virus was recovered not only from the respiratory organs but also from the spleen and kidneys. The other four mice survived for 14 days, and specific antibodies against H5 influenza virus were detected. All of the mice inoculated with Dk/Yokohama/03 and R(Dk/Mong-Dk/Mong) survived for 14 days. The virus was recovered only from the respiratory organs of the mice at day 3 p.i. It was found that the pathogenicity of these two viruses in mice was relatively low.

Table 6. Virus recovery and antibody response from miniature pigs inoculated with avian influenza virus

Viruses	Virus titers ($logTCID_{50}/ml$)							Antibody response[a] on 14 days p.i.
	1 day	2 day	3 day	4 day	5 day	6 day	7 day	
Ck/Yamaguchi/04 (H5N1)	–[b]	–	–	–	–	–	–	–
Dk/Yokohama/03 (H5N1)	–	–	–	–	–	–	–	–
R(Dk/Mong-Dk/Mong) (H5N1)	–	2.7	2.5	1.7	–	–	–	+

[a]Antibody detection was examined by ELISA. –: ELISA titer was below 40. +: ELISA titer was over 40

[b]–: <1.5 $logTCID_{50}/ml$

Miniature pigs

All of the miniature pigs inoculated with the three H5N1 viruses survived for 14 days. No virus was detected in the nasal swabs of the miniature pigs inoculated either with Ck/Yamaguchi/04 or Dk/Yokohama/03 from day 1 p.i. to day 7 p.i. (Table 6). In these two miniature pigs, sero-conversion to H5 influenza virus was not detected at day 14 p.i. In another experiment with miniature pigs inoculated with Ck/Yamaguchi/04, the virus was not recovered from any of the tissues at days 3 and 14 p.i. (data not shown). These results indicated that miniature pigs were not infected with Ck/Yamaguchi/04 and Dk/Yokohama/03. Although there were no disease signs in the miniature pig inoculated with R(Dk/Mong-Dk/Mong), viruses were recovered from the nasal swabs between day 2 p.i. and day 4 p.i. (2–4d). Sero-conversion to H5 influenza virus was detected in the miniature pig inoculated with R(Dk/Mong-Dk/Mong).

Discussion

The present study was conducted to determine the pathogenicity of Ck/Yamaguchi/04 in chickens, quails, budgerigars, ducklings, mice, and miniature pigs. Two H5N1 avian influenza viruses, Dk/Yokokama/03 and R(Dk/Mong-Dk/Mong), were compared in terms of pathogenicity with Ck/Yamaguchi/04. The intravenous pathogenicity index (IVPI) in 6-week-old chickens for Ck/Yamaguchi/04, Dk/Yokohama/03, and R(Dk/Mong-Dk/Mong) was 3.0, 2.7, and 0.0, respectively (data not shown). Based on the present results, Ck/Yamaguchi/04 and Dk/Yokohama/03 were classified as HPAI viruses and R(Dk/Mong-Dk/Mong) as a non-pathogenic virus by the OIE criteria [2]. Ck/Yamaguchi/04 and Dk/Yokohama/03 caused systemic infections in birds, but showed little or no pathogenicity in mammals. The slightly longer mean death time in chickens inoculated with Dk/Yokohama/03 allowed for the development of cyanosis of the wattle, typical signs of HPAI. The tendency was shown that virus of higher titer was recovered from chickens inoculated with Ck/Yamaguchi/04 than those inoculated with Dk/Yokohama/03.

The pathogenicity of Ck/Yamaguchi/04 and Dk/Yokohama/03 in quails and budgerigars was as high as that of the HPAI virus, Ck/Hong Kong/220/97 (H5N1), which caused an acute and lethal infection [21]. Notably, the pathogenicity of Ck/Yamaguchi/04 in the quails seemed to be higher than that of Dk/Yokohama/03, as evidenced by the mean death times (Ck/Yamaguchi/04 vs Dk/Yokohama/03, $P = 0.05$) and the tissues from which the viruses were recovered. This difference may be due to the adaptation of isolated HPAI viruses from different hosts (chicken and duck) to quails. The greater susceptibility of quails to the virus originating from duck than from chickens is consistent with previous reports [17]. In our another experiment, Ck/Yamaguchi/04 and Dk/Yokohama/03 caused systemic infections in wild starlings (*Sturnus cineraceus*) (data not shown), indicating that feral birds could play a role as intermediates in virus transmission among poultry flocks, thereby contributing to the spread of avian influenza virus as in the outbreaks in Australia [20]. During the outbreaks of H5N1 HPAI in Japan, 2004, viruses were

isolated not only from chickens but dead crows [18]. The possibility remains that avian influenza virus is spread by the contact of wild birds with chickens.

The pathogenicity of Ck/Yamaguchi/04 and Dk/Yokohama/03 for five-week-old ducks was not high compared to that for chickens and Dk/Yokohama/03 replicated more rapidly and efficiently in the multiple organs than Ck/Yamaguchi/04 in ducks [13]. In the present study, virus was recovered from multiple tissues of three-day-old ducklings inoculated either with Ck/Yamaguchi/04 or with Dk/Yokohama/03, and some of these ducklings were dead, indicating that the pathogenicity of these two viruses in three-day-old ducklings was high.

In the present study, virus was recovered from multiple tissues of only one mouse, which died at day 4 p.i. Two mice died after the inoculation of Ck/Yamaguchi/04 at an EID_{50} of $10^{8.0}$ and the mortality rate of mice was only 33% ($n=6$). In the latest publication, the 50% lethal dose of the same strain in mice was 5×10^5 EID_{50} under the same conditions (6-week-old female BALB/c mice via the intranasal route), and virus was also recovered from the brain [18]. The difference in pathogenicity may be due to the passage history of Ck/Yamaguchi/04 since the virus obtained from the National Institute of Animal Health (Japan) was propagated twice in embryonated chicken eggs before the present animal experiments. The pathogenicity of the H5N1 viruses isolated from humans in Hong Kong, 1997, was extremely high in mice [5, 7]. In the present study, more than half of the mice inoculated with Ck/Yamaguchi/04 survived the infection, indicating that the 50% mouse lethal dose was over $10^{8.0}$ EID_{50}. In conclusion, the pathogenicity of Ck/Yamaguchi/04 and Dk/Yokohama/03 in mice was much lower than that of the H5N1 viruses isolated from humans in Hong Kong, 1997.

Miniature pigs showed susceptibility to influenza virus, similarly to domestic pigs [3]. Miniature pigs were not susceptible either to Ck/Yamaguchi/04 or to Dk/Yokohama/03, but limited viral replication was observed in upper respiratory tissues in the miniature pigs inoculated with R(Dk/Mong-Dk/Mong). Therefore, the pigs may not play a major role in the maintenance and spread of Ck/Yamaguchi/04 and Dk/Yokohama/03. In contrast, H5N1 viruses isolated in 1997 from a boy (Hong Kong/156/97) and chicken (Ck/Hong Kong/258/97) replicated in pigs, although transmission through contact was not detected [24]. These results suggest that the susceptibility of pigs to avian influenza viruses has no relation to the pathogenicity of the strains in chickens or their subtypes, indicating that possible factors involved in host range restriction may be located in some gene segment(s) other than the HA gene [11, 23].

In conclusion, Ck/Yamaguchi/04 is highly pathogenic to birds and cause systemic infection, including brain. The results indicate that the susceptibility of pigs to this HPAI virus is very low, and that the possibility of genetic reassortments with this HPAI virus in pigs is not a concern.

Acknowledgments

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(H5N1) and A/duck/Yokohama/aq-10/03 (H5N1) influenza viruses, respectively. We also thank Dr. A. S. Mweene for discussing the contents of and English in this paper.

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医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-10

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 6 月 2 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	The public health risk from highly pathogenic avian influenza viruses emerging in Europe with specific reference to type A/H5N1. European Centre for Disease prevention and Control, scientific advice, June 1, 2006	公表国 スウェーデン	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
欧州の病原性トリインフルエンザウイルス(以下，HPAIVs)，特にトリインフルエンザ A（H5N1）型（以下 A/H5N1）によるヒトの健康へのリスクを評価している。野鳥と家禽での HPAIVs の世界的な大発生は 1990 年代より増加していて，現在欧州に及んでいる。1997 年までヒトへの感染は非常に少数であった。しかし，1997 年にアジアでヒトでの致死率が高く(50%以上)，遺伝子学上安定した A/H5N1 ウイルス株が出現したため，世界の保健当局は大きな懸念を示した。ヒト感染の主要ルートは重度に感染したトリとの直接接触，または調理されていないトリ食品の摂食である。現時点で，アジアで数件のヒト間での感染症例が報告されている。疫学データによると，A/H5N1 は最初に発見された時点と変わらずヒトに適応していないため，現在のウイルス型によって流行が引き起こされることはほとんどないと示唆された。欧州では実際，トリとヒトは地理的に隔離されているためヒトの健康への影響は非常に低い。対照的に，アフリカ，南アジア，中東では理論上のリスクは存在する。 A/H5N1 暴露によるヒトへの影響は不明確であるが，大規模な家禽に対する予防接種が高リスクの国々で行われた。 H5N1 ウイルスのヒトへの感染拡大予防のため、ECDC(途上国間地域経済協力)は以下を奨励している 1．野鳥と家禽の頻繁な調査 2．獣医と医療サービスの密接な協力 3．高リスクの人々への適切な情報と監査	BYL-2006-0234 www.ecdc.eu.int/influenza/update_influenza.php

報告企業の意見	今後の対応
インフルエンザウイルスに対する弊社の血漿分画製剤の安全性は，菌株の種類に関わらずウイルス不活化工程により確保されている。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

(3)

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TECHNICAL REPORT

ECDC SCIENTIFIC ADVICE

The Public Health Risk from Highly Pathogenic Avian Influenza Viruses Emerging in Europe with Specific Reference to type A/H5N1 Version June 1st 2006

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