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Guidance for the identification of bony lesions related to smallpox

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ABSTRACT

Objective: This research aimed to address the underrepresentation of smallpox (osteomyelitis variolosa) in palaeopathology, providing a synthesis of published literature and presenting guidance for the identification of osteomyelitis variolosa in non-adult and adult skeletal remains.
Materials and methods: Literature regarding smallpox and published reports of individuals with osteomyelitis variolosa were synthesised and critiqued to produce clear diagnostic criteria for the identification of smallpox osteologically.
Results: Associated osteological changes begin in non-adults, where skeletal morphology is rapidly changing. Characteristic lesions associated with non-adult osteomyelitis variolosa include inflammation and destructive remodelling of long-bone joints and metaphyses. Where childhood infection was survived, residual osteomyelitis variolosa lesions should also be visible in adults in the osteoarchaeological record.
Conclusions: Despite long-term clinical recognition, only limited osteological and archaeological evidence of osteomyelitis variolosa has yet emerged. With improved diagnostic criteria, osteomyelitis variolosa may be more frequently identified.
Significance: This is the first synthesis of osteomyelitis variolosa encompassing both clinical and palaeopathological literature, providing detailed guidance for the identification of osteomyelitis variolosa in skeletal remains. It will lead to the increased identification of smallpox osteologically.
Limitations: Differential diagnoses should always be considered. The archaeological longevity of smallpox, and the potential for archaeological VARV to cause clinically recognised smallpox, is currently unknown. Characteristic bone changes in the archaeological record may be other, extinct human-infecting-orthopoxviruses.
Suggestions for further research: Further consideration of the implications of age of smallpox contraction on bony pathology: whether epiphyses are affected differently due to state of fusion. Reassessment of individuals previously identified with smallpox-consistent lesions, but otherwise diagnosed.

1. Introduction

Smallpox is a communicable disease caused by the variola virus (VARV), which is estimated to have infected humans for circa 2000 years (Spinney, 2020). Smallpox is believed to have killed up to 500 million people in the 1900s alone and, until its eradication in 1980, continued to infect an estimated 15 million people each year across 30 countries (Koplow, 2003). Yet, despite the disease's longevity and reach, published physical evidence for smallpox in the archaeological record is limited to fewer than 20 individuals.

Sequencing of the modern VARV (mVARV) genome showed that VARV, an orthopoxvirus, emerged from a shared ancestor with the camelpox (CMLV) and taterapox (TATV) viruses just under 4000 years ago, likely pointing to a geographical origin in the Horn of Africa (Babkin and Babkina, 2015; Thèves et al., 2016; Mühlemann et al., 2020; Forni et al., 2023). mVARV, which is the cause of smallpox referred to in clinical literature, emerged around the 18th century and, at the time of smallpox's eradication, caused two forms of the disease: variola major and the less common, less virulent, variola minor (FDA, 2018). Where smallpox is endemic, particularly in areas where the variola-minor strain is most prominent, it is considered a childhood disease (Lewis, 2018).

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Two other VARV clades are known from DNA evidence to have evolved and become extinct prior to the emergence of mVARV, known as historic VARV (hVARV) and ancient VARV (aVARV) (Mühlemann et al., 2020; Forni et al., 2023; Fig. 1). hVARV emerged around the 16th century CE and has been identified in a 17th century non-adult mummy from Lithuania (Duggan et al., 2016), an 18th century adult mummy from Siberia (Biagini et al., 2012), and an 18th century non-adult skeleton from France (Meffray et al., 2021). aVARV likely emerged around the 6th century CE and was only related to the younger clades through their common ancestor almost 4000 years ago (Mühlemann et al., 2020; Forni et al., 2023). This early VARV was potentially less virulent than the later VARV clades (Mühlemann et al., 2020; Forni et al., 2023), meaning it may be more observable in archaeological samples, but some critics argue that, whilst it was clearly a human-infecting-orthopoxvirus, it may be misleading to call it smallpox (Newfield et al., 2020; 2022). Nevertheless, the same critics estimate that a VARV capable of causing smallpox could have emerged from around the 4th century CE (Newfield et al., 2022), demonstrating how an improved understanding of the disease-manifestations is still relevant to the archaeological record. Despite this estimation, no evidence of any VARV DNA has been identified predating the turn of the 7th century CE, yet multiple historical sources document potentially attributable earlier epidemics (Littman and Littman, 1973; Maddicott, 1997, 2006; Kotar and Gessler, 2013; Philbrick, 2014; Thèves et al., 2016; Fig. 1) and characteristic skin lesions have been observed on three Egyptian mummies dating to between 1580BCE and 1100BCE (Ruffer and Ferguson, 1910; Thèves et al., 2016).

As observed in mummified remains (Ruffer and Ferguson, 1910), where soft tissue is present, smallpox is generally recognisable from its characteristic pustular rash, as well as accompanying fever in living patients (Aufderheide and Rodriguez-Martin, 1998). But significant involvement of the skeleton has also been clinically documented and should not be overlooked. Skeletal involvement following smallpox infection, known as osteomyelitis variolosa, is generally seen once pustules begin to clear. The condition is estimated to affect 2–20% of children with smallpox (Cockshott and MacGregor, 1958; 1959; Davidson and Palmer, 1963) and is attributed when diagnostic characteristics and distribution of skeletal changes are observed, typically involving the elbows, with less frequent involvement of the wrists, knees, and ankles (Cockshott and MacGregor, 1958; 1959; Davidson and Palmer, 1963; Eekels et al., 1964; Khurana et al., 2019). As such, given this characteristic appearance, it is plausible that smallpox can be identified in individuals from archaeological contexts.

In the archaeological record, fewer than ten skeletal individuals with potential smallpox bone involvement have so far been identified. These individuals were recovered from France, England, Canada, Portugal, and the United States of America, and date approximately to between the 10th and 19th centuries (Table 1). Despite the eradication of smallpox in 1980 (MacIntyre, 2020), clinical reports continue to document skeletal abnormalities linked to childhood smallpox infection. At least ten such reports have been published in India alone since 2011 (Tang et al., 2021), showing the need for improved understanding of the long-term skeletal changes associated with the disease, even in a post-eradication world. Considering the frequency of smallpox diagnoses amongst living individuals still being reported, the prevalence of individuals documented since the 1800s by Cockshott and MacGregor (1958), and confirmation that VARV DNA has been present in humans as far back as the 7th century (Mühlemann et al., 2020), there appears to be a gross underrepresentation of smallpox within the osteoarchaeological record.

Indeed, amalgamating the literary, archaeological, and osteological data regarding smallpox (Fig. 1) demonstrates the longevity, frequency,

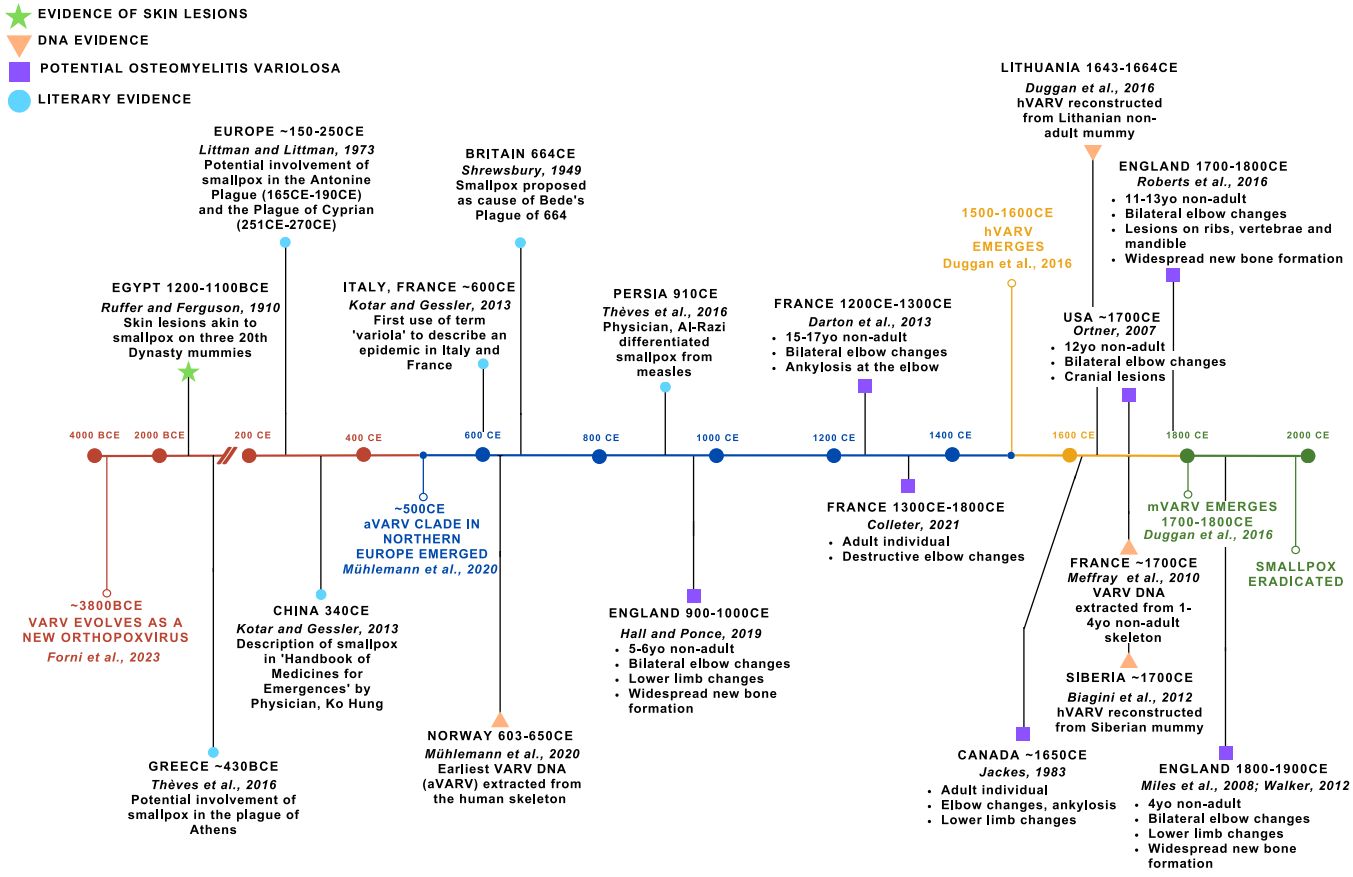

Fig. 1. Potential evidence for smallpox in the archaeological record since the arrival of VARV (not exhaustive), (Ortner, 2007; Shrewsbury, 1949).

Table 1
Smallpox in the archaeological record: Published Skeletal Evidence.

Identification code	Archaeological Site Location	Site Date (CE)	Age-at-death estimation	Skeletal changes	Reference
MBH04 [768]	St Marylebone Old Church	1750-1851	4 years	Bilateral elbow involvement (diaphyseal necrosis, destruction of lateral epicondyles, bone formation, destruction of left ulnar articular surface, osteomyelitis, periostitis), woven bone on right scapula and proximal left tibia	Miles et al., 2008 Walker, 2012
Burial 69	Coach Lane, North Shields	1711–1857	11.5-13.5 years	Elbow involvement (extensive woven bone deposits on long bones; destructive lesions on metaphyseal surfaces of the distal humerus and proximal radius), new bone formation on shoulders, destructive vertebral lesions, lytic lesions on left ribs, new bone formation on tibiae and femora, pelvis, clavicles, and right scapula	Roberts, 2016 Roberts et al., 2016
National Museum of Natural History, USA catalogue no. 377912	Mummy Caves, Kagamil Island, Alaska	Pre 1750	12 years	Bilateral elbow involvement (osteomyelitis, periostitis, cortical destruction in the metaphysis), lesions on the frontal bone	Ortner, 2003 Ortner, 2007
Skeleton Fe 1/33	Grimsby Cemetery, Ontario, Canada	1640-1650	Young adult	Abnormalities of hips and femora, elbow joint involvement (bony ankylosis of left humerus and ulna with corresponding flail joint, periostitis of left humerus, right elbow too fragmented to assess pathology)	Jackes, 1983
-	Sarilhos Grandes, Portugal	14th – 19th century	30-49 years	"Complete and asymmetrical destruction of the articular surfaces of the left elbow joint… marked underdevelopment of the left upper limb"	Magalhães et al., 2021 (conference abstract)
-	Convent of Jacobins of Rennes, France	Late 14th – 18th century	20-49 years	Severe destruction and remodelling of at least one elbow joint. Pathology is not further discussed as this case is not the focus of the paper.	Colleter, 2021
-	Aubeterre-sur-Dronne, Charente, France	Ossuary dating from 11th – 19th century	-	"Incomplete left humerus and ulna fused at the elbow joint in semi-flexion position"	Coqueugniot et al., 2022 (conference abstract)
Skeleton 833	Pont-sur-Seine, Aube, France	1022-1155	15-17 years	Bilateral elbow involvement (enlarged metaphyses, bony ankylosis of right humerus and ulna, elongation of right lateral epicondyle and resorption of lateral condyle, bilateral elongation of radial necks, left elbow shows flail joint and necrosis of the articular surface)	Darton et al., 2013
Burial 2639	Soham, Cambridgeshire	10th century	5-6 years	Widespread periostitis inc. bilateral woven bone deposits on upper and lower limbs focused near the joints, left scapula and right clavicle, bilateral elbow involvement (porous bone deposits on humeri and radii, enlarged left ulna – potential ankylosis during life but broken post-mortem)	Hall and Ponce, 2019 (conference poster)

and severity of smallpox and its potential impact on past populations. Smallpox has been suggested as the cause of ancient epidemics as far back as the 5th century BCE, such as the Antonine Plague (2nd- 3rd century CE), and Bede's Plague (7th century CE) (Littman and Littman, 1973; Maddicott, 1997, 2006; Fig. 1), and by the 18th and 19th centuries, smallpox was such a central concern that work was being undertaken to model its life expectancy and survival rates (Bernoulli, 1766, based on Halley, 1693; Daw, 1979). The implications of smallpox were readily acknowledged, and inoculation subsequently encouraged. However, the osteological record is yet to reflect the scale of these smallpox epidemics and infections. Consequently, this research aims to target this osteological underrepresentation, informing future palaeopathological diagnoses by providing clear, up-to-date guidance for the identification of osteomyelitis variolosa in both non-adult and adult skeletal remains. This research also aims to highlight briefly the ways in which understanding of smallpox's ability to impact the skeleton may continue to be relevant for modern medicine. For example, the presence of active VARV samples in US and Russian laboratories leaves an ongoing threat of disease reintroduction, either by accidental leak or weaponization (Alibeck, 2004; CDC, 2018; MacIntyre, 2020). Should an outbreak of smallpox occur, improved understanding of its impacts on the human skeleton could contribute to the planning of both short and long-term medical responses.

Moreover, there is a need for improved understanding of how other human-infecting poxviruses, such as the mpox virus (MPXV), could also impact humans in the long-term. MPXV is another orthopoxvirus, which shared a common ancestor with VARV 8000 years ago. Between 2018 and 2021, 12 individuals with MPXV were reported outside of Africa, all connected to travel or animal imports from the African continent (CDC, 2023). Potentially linked to rising temperatures and disruption of ecosystems (Hoberg and Brooks, 2015; Roberts et al., 2018; Oladoye, 2021), reports of mpox outside of Africa have continued to increase dramatically (WHO, 2021). Between January 2022 and November 2023, 89,447 confirmed cases of mpox (including paediatric cases) were reported across 109 countries that had not historically reported mpox (CDC, 2023). As the SARS-COV-2 pandemic has demonstrated, the long-term health impacts of viral infections can be debilitating and place great strain on public services, especially when said impacts were previously unknown (Bouza et al., 2005; Tao et al., 2020; Lopez-Leon et al., 2021; Cutler, 2022). It goes without saying, then, that an understanding of mpox's long-term impacts on the human body is vital for informed development of appropriate medical and political responses to future mpox outbreaks. Furthermore, 20th century studies suggest that another orthopoxvirus, vaccinia virus (VACV: a collective term for the varying orthopoxvirus strains used in smallpox vaccinations throughout history), can also lead to similar bone involvement and changes as seen in smallpox (Kini and Kesavaswamy, 1941; Sewall, 1949; Cockshott and MacGregor, 1958; Elliot and Edin, 1959; Silby et al., 1965). The potential then for mpox to cause comparable bony changes must be considered, especially as initial reports have already indicated a relationship with osteomyelitis and joint inflammation (Fonti et al., 2022; Lombès et al., 2023). An understanding of how other orthopoxviruses (namely smallpox) impact the human body in the long term is an ideal starting point. Consequently, this publication aims to provide a synthesis of the archaeological and clinical evidence for skeletal involvement in smallpox, providing information about the expected skeletal changes at different stages following infection and the skeletal aspects most involved.

2. Prevalence and types of skeletal involvement typical of smallpox

The earliest mentions of smallpox-related osteomyelitis are in clinical reports of living patients (predominantly children) and necroscopies dating from the 19th and early 20th centuries (e.g., Neve, 1887; Chiari, 1893; Bancroft, 1904; Brown and Brown, 1923; see Cockshott and MacGregor, 1958, for a review of early 20th century reports). By the 1920 s, clinical reports had documented that smallpox-related bone involvement was not uncommon (Mehta, 1927) and amongst local people of the Philippine Islands, bone involvement was a known and dreaded complication of smallpox (Sison and Musgrave, 1910).

In the mid-20th century, several large radiographic studies of living patients emerged. These studies indicated that up to 20% of children with the variola virus would develop a characteristic set of skeletal changes (osteomyelitis variolosa) within weeks of infection (Davidson and Palmer, 1963). Skeletal lesions were primarily focused on and around the joints and long bones, and most commonly the elbows (Cockshott and MacGregor, 1958, 1959; Davidson and Palmer, 1963; Eekels et al., 1964). Working in Nigeria during the 1957 smallpox epidemic, Cockshott and MacGregor (1958; 1959) observed 34 children with osteomyelitis variolosa in hospital over a period of 18 months; this was out of a total of 2500 individuals with smallpox (adults and non--adults). Thus, they estimated that roughly 0.25–0.5% of all smallpox sufferers, and 2–5% of children with smallpox, were liable to bone involvement. Davidson and Palmer, however (1963), documented a much higher prevalence of osteomyelitis variolosa amongst individuals under observation in the Lilongwe district of modern-day-Malawi. They reported that 82/400 (20.5%) individuals with smallpox, all children, developed bone involvement. It is not clear whether these varying prevalence rates were caused by different strains of VARV, but increased severity in bone involvement was documented in unvaccinated children (Cockshott and MacGregor, 1958; Davidson and Palmer, 1963).

All incidences of new bone involvement were observed in children between the ages of 9 months and 14 years (Cockshott and MacGregor, 1958; 1959; Davidson and Palmer, 1963). As the condition appears only to begin manifesting prior to skeletal maturity (before fusion of the long bones) (Jackes, 1983; Davidson and Palmer, 1963), this may point to its spread being impacted by changes to epiphyseal anatomy and blood supply with age (Cockshott and MacGregor, 1959). Whilst it is unknown if certain individuals are more likely to suffer from bone involvement than others (Davidson and Palmer, 1963), anaemia and protein malnourishment have been suggested as potential predisposing factors (Cockshott and MacGregor, 1958; Eekels et al.,1964).

In palaeopathological literature, both the lower range of 2–5% and the full range of 2–20% (of children with smallpox developing osteomyelitis variolosa) have been accepted by different authors (Ortner and Putschar, 1981; Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003; Powers, 2012). But even the full range is based only upon smallpox patients in hospitals or under clinical observation, and therefore may overlook patients whose bone involvement remained unnoticed by physicians, or individuals that did not or could not access medical attention. Thus, incidence of bone involvement in smallpox may be higher. Moreover, any subtle or earlier pathological skeletal involvement, apparent on dry bone (Ortner, 2003) and in computed tomography (CT) images (Pineda et al., 2009), may not have been visible on the 1950 s and the 1960 s radiographs.

Even so, these 20th century radiographic findings have since provided a basis for the identification of osteomyelitis variolosa up to the present day and have highlighted typical shorter-term and longer-term osteological sequelae of smallpox (Table 2; Figs. 3, 5).

2.1. Short term sequelae

Skeletal involvement is first seen between one and six weeks after the onset of smallpox infection. Some studies have reported that this is around the time that the characteristic skin lesions are beginning to clear (Cockshott and MacGregor, 1959; Davidson and Palmer, 1963), but it has also been suggested that bone involvement may begin sooner and remain masked until general malaise subsides (Gupta and Srivastava, 1973). Three separate pathways of involvement are presented by Resnick and Niwayama (1995):

1. Bilateral nonsuppurative osteomyelitis with necrosis: This usually involves gross periosteal thickening and reactive bone formation (Shah et al., 2013) and is likely directly caused by VARV (Brown and Brown, 1923; Cockshott and MacGregor, 1958).

Table 2
Summary of the approximate timings of osteomyelitis variolosa development, as described by Cockshott and MacGregor (1958; 1959). Asterisks mark where timing has been inferred.

Time since smallpox infection	Osteological sequelae
1-2 weeks	• Periosteal inflammation • Band of bone destruction visible around the physis • Inflammation of the metaphysis • If no secondary epiphyseal centre has yet formed, due to the age of the individual, a cap of bone distal to metaphyseal bone destruction may remain • Patchy destruction of carpal and tarsal bones* • Displacement and/or destruction of the epiphyses, with distension of the joint capsules*
2-3 weeks	• Further destruction of metaphyseal bone • Pronounced periosteal new bone formation • Involucrum formation, often spanning the length of the entre bone shaft (generally limited by the capsular attachments) • Bone spurs may form briefly, particularly on the distal humerus • Sclerosis and periosteal new bone formation on the carpal and tarsal bones*
3-4 weeks	• Original diaphysis may appear sequestered within the involucrum, but is not generally expelled as dead bone • Original diaphysis gradually assimilated into the periosteal involucrum
4 weeks – 1 year	• Diaphyseal involucrum may continue to be present (seeCockshott and MacGregor, 1959: 60) • Remodelling of limbs seen to occur after around 1 year in younger children and original bone shaft no longer distinguishable from the new bone • Bones heavily affected generally remain thicker than normal
1 year + (labelled as 'late manifestations' in the literature, but timing never explicitly defined)	• Affected carpal and tarsal bones remain enlarged in size and density for at least one year • Weight bearing & activity may lead to further abnormality • Formation of flail joints, often with loose bodies • Fibrous or bony ankylosis • Degenerative secondary osteoarthritis • Malformation of bones over time, intact joint space • Delayed growth • Delayed appearance/disappearance of secondary centres of ossification • Premature epiphyseal fusion • Distortion by weight bearing

2. Secondary suppurative arthritis: Bacterial infection of the joints, likely due to lowered immunity after smallpox infection (Brown and Brown, 1923). Cockshott and MacGregor stated that this was an increasingly rare complication when writing in 1958.
3. Multifocal non-suppurative arthritis (inflammatory joint modification following extra-articular infection: Plesca et al., 2013), commonly appearing bilaterally.

The first pathway can be seen on radiographs as a transverse band of bone destruction (radiolucency) in the metaphyses of long bones, sharper and more defined on the epiphyseal side (Fig. 2; Cockshott and MacGregor, 1958; Davidson and Palmer, 1963). Cockshott and MacGregor (1958) note that this variola metaphyseal involvement differs from similar pyogenic involvement in that it traverses the bone as a band from the onset, as opposed to beginning on one side of the bone and subsequently spreading to the other. This early involvement (roughly the first 1–2 weeks) is most clear in the proximal radii, followed by the proximal ulna and distal humerus (Fig. 3; Cockshott and MacGregor, 1958; 1959). Epiphyseal destruction and displacement follow, likely occurring because of metaphyseal infection (Fig. 2; Cockshott and MacGregor, 1958; Davidson and Palmer, 1963). This phenomenon often appears on radiographs as loose bodies within swollen joint capsules (Cockshott and MacGregor, 1958; 1959: radiograph pg 58; Davidson and Palmer, 1963).

Destruction of the epiphyses has been described as osteomyelitis variolosa's *"most unique feature"* and is almost exclusively seen in younger children (Cockshott and MacGregor, 1958: 382). The epiphyseal regions are most active at this age, and so it was hypothesised that the destruction may be caused by an attack on proliferative (rapidly dividing) epiphyseal cartilage cells (Cockshott and MacGregor, 1958). From their radiographic observations, Cockshott and MacGregor (1959) observed that the most recently formed epiphyses seemed to be those most vulnerable to displacement and destruction. Recently formed and forming epiphyses are those where epiphyseal cartilage cells are most present and actively proliferating. But in more mature epiphyses, cartilage cell division is slowed, and the once proliferating cells transition to allow for cartilage mineralisation (Ağırdil, 2020). In the youngest children, where epiphyses have not yet developed, *"a thin cap of intact bone"* appears to remain on the epiphyseal aspect of the metaphysis and destruction occurs on the diaphyseal aspect (Cockshott and MacGregor, 1958: 380).

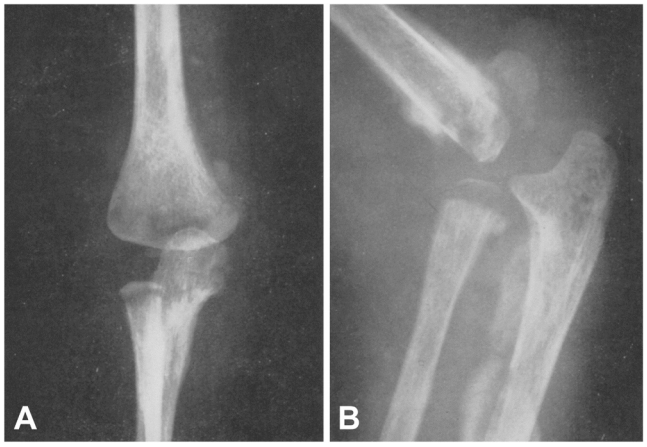

Fig. 2. Radiographs of smallpox patients admitted to University College Hospital, Ibadan, Nigeria, 1957. A) The right elbow of a one-year-old, taken four days after appearance of bone involvement. Clinical report notes transverse bands of metaphyseal inflammation and periostitis. B) The left elbow of a one-year-old, two weeks after onset of bone involvement. Clinical report notes displacemnt of the humeral epiphysis and severe periosteal reaction with involucrum. Reprinted from *The Journal of the Faculty of Radiologists*, 10(2), Cockshott, P. and MacGregor, M., 'The Natural History of Osteomyelitis Variolosa', Pages 59–61., Copyright (1959), with permission from Elsevier.

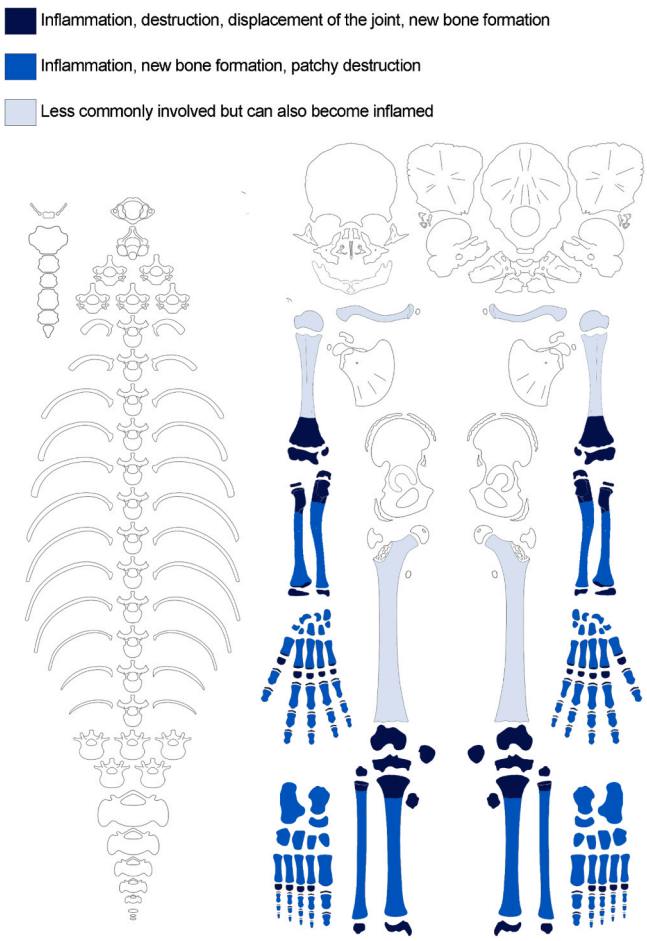

Fig. 3. Typical early-stage (short-term) bone involvement associated with osteomyelitis variolosa.
Non-adult recording form adapted from Hodson (2022).

Destruction at the joints is generally accompanied by a marked periosteal reaction spreading along the bone shaft (Davidson and Palmer, 1963; Eekels et al., 1964). As it progresses, this spread can lead to the formation of diaphyseal involucre, stretching the entire length of the bone shaft in severe infections (Fig. 4; Davidson and Palmer, 1963). By the third and fourth weeks of skeletal involvement, Cockshott and MacGregor (1959) state that the bone diaphysis may seem sequestered within the involucrum, as in untreated pyogenic osteomyelitis (Fig. 4). Differing from pyogenic osteomyelitis, however, is the generally bilateral appearance of bone involvement in osteomyelitis variolosa, often affecting both the arms and the legs simultaneously. In pyogenic osteomyelitis, the simultaneous involvement of more than one bone is rare without a comorbid underlying condition (Sipahioglu et al., 2014).

Archaeologically, three out of the seven published individuals with suspected osteomyelitis variolosa, describe bone changes typical of short-term involvement; these are all individuals estimated to be under 10 years-of-age (Table 1: Miles et al., 2008; Walker, 2012; Ortner, 2003; Hall and Ponce, 2019). A fourth individual (Roberts et al., 2016) may also present bone changes consistent with early-stage osteomyelitis variolosa; however, the skeleton simultaneously exhibits pathological lesions more typical of other conditions, which could obscure stage-identification.

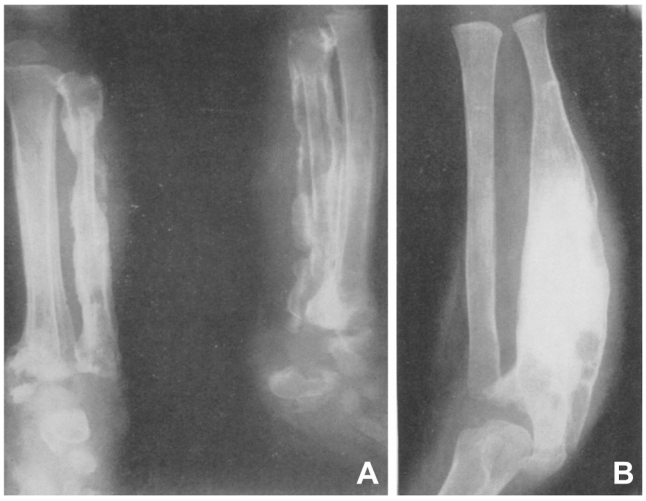

Fig. 4. Radiographs of smallpox patients admitted to University College Hospital, Ibadan, Nigeria, 1957. A) Bilateral periosteal involucra spreading the length of the tibiae and fibulae and ankle joint involvement, in a two-year-old child, roughly one month after infection onset. B) Severe involvement of the forearm and elbow joint in a two-year-old child, two months after infection onset. Reprinted from *The Journal of the Faculty of Radiologists*, 10(2), Cockshott, P. and MacGregor, M., 'The Natural History of Osteomyelitis Variolosa', Pages 59–61., Copyright (1959), with permission from Elsevier.

2.2. Long term sequelae

Later manifestations of smallpox include flail joints (instability, loss of function, and loss of control in flexion or extension at joint; Inglis et al., 1997; Kumar et al., 2021), premature epiphyseal fusion due to necrosis, distortion, malformation of bones, and ankylosis (Fig. 5; Cockshott and MacGregor, 1959; Davidson and Palmer, 1963). Generally, these changes occur when short term joint involvement leads to abnormal joint mobility and subsequently secondary, degenerative arthritis. Fibrous and/or bony ankylosis with acute arthritis is a less common long-term sequela, likely caused by damage to articular cartilage by secondary bacterial infections (Fig. 6; Cockshott and MacGregor, 1958). It has been suggested that these secondary infections may occur due to reduced immunity after smallpox, with bacteria entering through sinuses or viraemia from infected skin lesions (Cockshott and MacGregor, 1958).

These later manifestations of smallpox can be found in children and adults alike. However, across all currently published clinical literature, osteomyelitis variolosa involving severe bone malformation and ankylosis, is exclusively found in individuals who suffered from smallpox over a decade prior (Sison and Musgrave, 1910; Cockshott and MacGregor, 1959; Margolis, et al., 1978; Arora et al., 2008; Singh, 2010; Andrews and Jayan, 2011; Nema et al., 2011; Purandarnath and Douraiswami, 2011; Mugalur et al., 2015; Khurana et al., 2019; Tang et al., 2021). The earlier signs of these later manifestations, though, such as delayed growth, premature fusion of epiphyses causing stunted bone growth, and distortion due to weight bearing, may appear much sooner (Cockshott and MacGregor, 1958).

Later manifestations have been reported clinically in over a dozen individuals (all regarding living individuals aged 15 or over, e.g., Cockshott and MacGregor, 1959; Margolis et al., 1978; Balachandar and Narayana Reddy, 2015; Khurana et al., 2019), with most affected individuals being Indian adults who had suffered from smallpox during the 1972 epidemic. A review by Khurana et al. (2019), showed that severe, bilateral involvement of the elbows was most common, followed by involvement of the hands and feet (dactylitis), and ankles.

Archaeologically, bone abnormalities characteristic of later smallpox manifestations are present in three published individuals: a 15–17-year-old (Skeleton 833) from Pont Sur Seine, Aube (Darton et al., 2013), an adult individual (Skeleton Fe 1/33) from Grimsby Cemetery, Ontario (Jackes, 1983), and a 20–49-year-old individual from the Convent of Jacobins of Rennes, France (Colleter, 2021). All these individuals exhibited severe destructive involvement of the elbows, including necrosed distal humeri with absent capitula and extension of the medial epicondyles, distortion/elongation of the radial neck, and evidence of a humeroulnar flail joint (Cockshott and MacGregor, 1959; Jackes, 1983; Darton et al., 2013; Colleter, 2021). Some individuals also showed altered morphology of the proximal ulnae with extension of the sigmoid cavity, olecranon process, and coronoid process (Jackes, 1983; Darton et al., 2013). The individual known as Skeleton 833 exhibited bony ankylosis of the right elbow.

2.3. A brief discussion on age and diagnosis

The most common age range for those with typical short-term sequelae, according to clinical studies from the 1960 s, is between 1 and 5 years (67% of non-adults with smallpox; Davidson and Palmer, 1963; and Jaffari and Hussain, 1969). A smaller number of cases was also documented in infants up to 1 year of age (13%; Davidson and Palmer, 1963), and non-adults between the ages of 6 and 10 years (13%; Davidson and Palmer, 1963). Following the general trend, neither Davidson and Palmer (1963) nor Jaffari and Hussain (1969) reported early-stage osteomyelitis variolosa in individuals over the age of 15 years (Davidson and Palmer, 1963; Jaffari and Hussain, 1969).

Short-term changes are very rarely observed in skeletally mature individuals, with only 6 published reports, dating from 1875 to 1938 (Banerjee, 1952; Cockshott and MacGregor, 1958). These include a report of an 18-year-old woman treated in hospital for bilateral osteological lesions and swelling of the elbows and knees shortly after smallpox (Cockshott and MacGregor, 1958), and a 21-year-old man with osteomyelitis of the clavicle and both radii 18 months after smallpox (Kolaczek, 1875). Given the time since smallpox infection, and the involvement of the clavicle, comparison with other clinical reports indicates that the latter individual may have been suffering from a secondary, pyogenic infection (Table 3). A further three individuals, all over the age of 20 and with joint involvement following smallpox, were also considered to have had pyogenic osteomyelitis infections, as opposed to osteomyelitis variolosa, due to the appearance of bony lesions on radiographs (Banerjee, 1952; Cockshott and MacGregor, 1958). It was concluded that the bone involvement was likely caused by bacterial infection following lowered immune resistance after smallpox. Consequently, it seems that where smallpox-related bone involvement occurs, according to the second pathway outlined by Resnick and Niwayama (1995), it can develop in non-adults and adults alike, the latter being more likely where smallpox is not endemic; this hypothesis has not been addressed in the clinical literature.

Fundamentally, the potential for diagnosis of smallpox-related bony lesions in adults should not be overlooked. Whilst it is extremely rare for an adult individual to exhibit short-term sequelae, when these lesions are present, smallpox should still be considered alongside other differential diagnoses; this may be especially pertinent for smallpox in the archaeological record, as the disease is less likely to have been endemic, thus potentially affecting adults more significantly than is reported in modern clinical literature. Particular focus ought to be placed on familiarisation with the typical long-term changes associated with the disease, especially as recent clinical literature continues to demonstrate the prevalence of the condition amongst childhood smallpox survivors. Whilst the expected later-stage lesions are generally still known to be bilaterally presenting, it should be considered that secondary pyogenic infection may also manifest on some skeletal elements unilaterally, as seen in the older clinical literature (Table 3).

Unfortunately, as the large clinical studies from the mid-20th century never produced any follow up reports regarding how the children (and their skeletons) appeared as they aged, no published literature provides

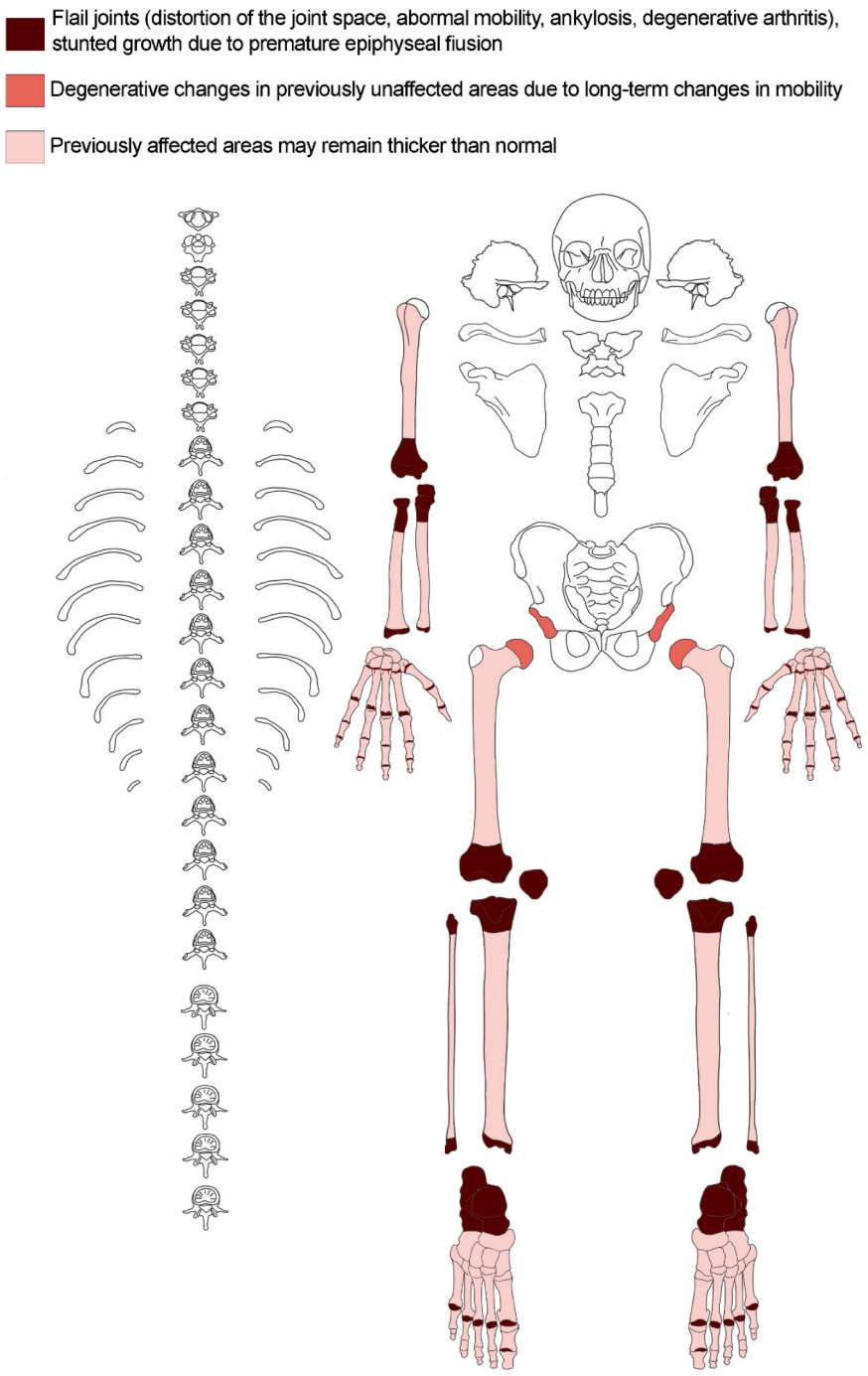

Fig. 5. Typical later-stage (longer-term) bone involvement associated with osteomyelitis.

a clear timeframe for the progression of osteomyelitis variolosa from the typical short-term to long-term manifestations. Based on observations of a single 15-year-old individual described by Cockshott and MacGregor (1959), progression may take anywhere from 1 to 10 years after onset of infection (Cockshott and MacGregor, 1959). Consequently, age-at-death and the stage of osteomyelitis variolosa progression cannot accurately be corroborated to indicate age at onset of infection.

In the absence of further research, as the clinical literature believes VARV may target proliferating epiphyseal cells, the most severe changes are likely to occur around the most active epiphyses at the time of smallpox infection (Cockshott and MacGregor, 1958). For example, short-term involvement is most common in children under 5 years-of-age and usually begins in the proximal radius, which develops its secondary ossification centre (where cells will be actively proliferating) between 3 and 5 years-of-age (Elgenmark, 1946; Cockshott and MacGregor, 1958; Garn et al., 1967; DeFroda et al., 2017). This hypothesis could explain how some short-term changes have been reported in young adults, as the distal radii and ulnae may not fuse completely until around 20 years-of-age (Schaefer, 2008), the medial epicondyle of the humerus until 13–18 years-of-age (Sahni and Jit, 1995; Coqueugniot and Weaver, 2007), and the distal femur and proximal tibia until approximately 20 years-of-age (Coqueugniot and Weaver, 2007; Cardoso, 2008). Moreover, periods of physical and psychosocial stress, and other chronic health conditions are known to delay skeletal maturation (Cavallo et al., 2021), further extending the possible timeframe for the development of short-term bone involvement in smallpox. Perhaps then,

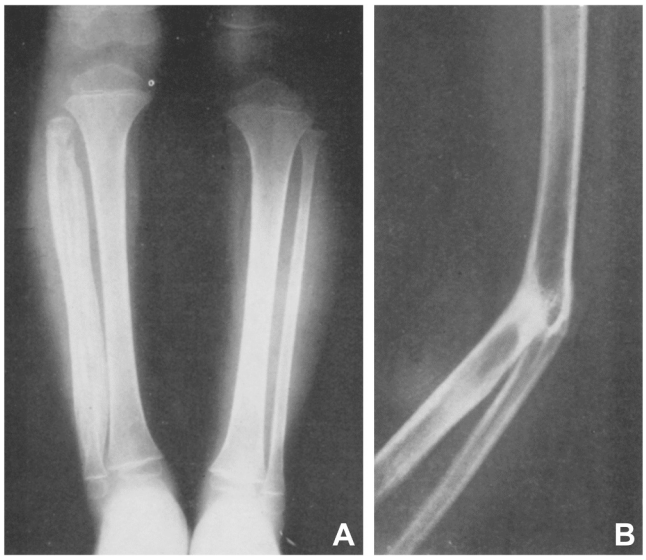

Fig. 6. Radiographs of smallpox patients admitted to University College Hospital, Ibadan, Nigeria, 1957. A) Lower limb involvement in a three-year-old child, roughly one year after onset of infection. B) Elbow joint in an individual who suffered from smallpox thirteen years prior, displaying bony ankylosis. Reprinted from *The Journal of the Faculty of Radiologists*, 10(2), Cockshott, P. and MacGregor, M., 'The Natural History of Osteomyelitis Variolosa', Pages 59–61., Copyright (1959), with permission from Elsevier.

we could roughly ascribe an age-at-onset based on epiphyses involved, whilst still appreciating that the elbows are likely to have been the longest affected joint (Cockshott and MacGregor, 1958).

In sum, it would be most useful to view smallpox bone involvement on a scale of progression. Skeletal involvement may fall anywhere along this scale but should generally, roughly correlate with the changes expected at the individual's age-at-death. I.e., all individuals aged 18-years would be expected to exhibit later-stage bone involvement, but an 18-year-old individual who suffered from VARV four years prior would likely show skeletal changes consistent with shorter-term involvement in comparison to an 18-year-old individual who experienced VARV 17-years prior. The latter individual would be expected to show much more extended, longer-term bone involvement.

3. Lesion Distribution and Secondary Diagnoses

When identifying disease from the skeleton, observing lesion distribution is as important as assessing the types of lesions exhibited (Ortner, 2008; Roberts and Manchester, 2010; Roberts, 2020). This is because pathological skeletal changes are often non-specific: similar bone changes could have multiple aetiologies (Roberts and Manchester, 2010). This is particularly the case for smallpox, where specific lesions are limited, and interpretation is complex: please refer to Figs. 3 and 5, and Table 3, for a summary of the types and distribution of bone changes associated with smallpox. Furthermore, assessment of lesion distribution provides a more complete picture of how an illness affected the skeleton and may have targeted different areas, which can subsequently be corroborated with clinical and palaeopathological literature to suggest potential diagnoses. The potential for a skeleton to exhibit changes from multiple conditions simultaneously should also be acknowledged (Roberts and Manchester, 2010). For changes typical of smallpox, potential differential diagnoses may include tuberculosis, treponemal disease, leprosy, and rheumatoid arthritis (Gupta and Srivastava, 1973; Ortner and Putschar, 1981; Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003; Waldron, 2009; Purandarnath and Douraiswami, 2011; for a review of differential diagnoses see Tang et al., 2021: 8).

3.1. Upper Limbs

Involvement of the arms (namely the elbow joint, but also the wrists) is the most frequently accepted skeletal indicator of smallpox infection (Cockshott and MacGregor, 1959; Davidson and Palmer, 1963; Ortner and Putschar, 1981; Resnick and Niwayama, 1995; Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003, 2008; Singh, 2010; Nema et al., 2011; Khurana et al., 2019). In reports presented by Cockshott and MacGregor (1958; 1959), and Davidson and Palmer (1963), elbow involvement was documented in 80% of smallpox patients displaying bone involvement, and bilaterality was a key feature, which Cockshott and Macgregor (1958) stated was present on radiographs even when the condition was presenting unilaterally externally. Reflecting this, all published archaeological incidences of osteomyelitis variolosa present abnormalities of one or both elbows (Table 1). It is worth noting, though, that whilst this may be a true representation of how osteomyelitis variolosa presented in the past, it is also likely due to the palaeopathological expectation that the elbows should always be involved.

Bilateral involvement of the elbows is a characteristic that Ortner (2008: 211) states is a crucial diagnostic feature of skeletally manifested smallpox: "this distribution is very unusual and, when encountered in an archaeological human burial, a diagnosis of smallpox is likely''. This is reflected in the clinical literature. However, it is important to note that bilateral elbow involvement has also been observed (albeit rarely) in non-adults with tuberculosis (Table 3) (Dhillon et al., 2012), so proper attention should be paid to accompanying bone lesions and diagnoses should remain cautionary. The involvement of all three arm bones is another crucial feature of osteomyelitis variolosa, with the earliest involvement most prominent in the proximal radius and ulna (Cockshott and MacGregor, 1958). Differential diagnoses for elbow joint involvement may also include treponemal disease (more common in yaws or bejel than syphilis: Ortner, 2003; Waldron, 2009), and rheumatoid arthritis (one case of osteomyelitis in an adult, which was previously misdiagnosed as rheumatoid arthritis has been reported: Purandarnarth and Douraiswami, 2011). Whilst generally rare (Cockshott and MacGregor, 1958; Andrews and Jayan, 2011), severe involvement of the shoulders (inflammation and septic arthritis) has been documented in early clinical reports (Neve, 1887; Mehta, 1927), though these were highly suppurative and necrotic, therefore may be more indicative of secondary bacterial infection (Cockshott and MacGregor, 1958).

The reason for elbow predilection is currently unknown. However, Cockshott and MacGregor (1958) propose that strain and stress at the physis, whilst VARV is in the bloodstream, may leave the physeal region vulnerable to selective attack from the VARV virus (Cockshott and MacGregor (1958)). They suggest that the increased range of movement in two planes at the elbow and knee, compared with the distal limb joints, and decreased movement of the legs in comparison to the arms during active smallpox infection (due to illness), may be why the elbows appear to be targeted before the other joints (Cockshott and MacGregor, 1958).

3.2. Lower Limbs

Involvement of the lower limbs in smallpox infection has often been overlooked in palaeopathology, which is understandable given the increased frequency of bilateral arm involvement in smallpox and its uniqueness to the condition. It is important to highlight that lower limb involvement does occur and may not always be secondary to arm involvement. For example, Davidson and Palmer (1963) report that bilateral gross and florid new bone formation on the tibiae and fibulae may be sufficient to suggest a smallpox diagnosis, even in individuals where the elbow is unaffected (this was based on observations of live individuals). This is particularly pertinent when assessing osteoarchaeological remains, as the upper limbs may be fragmented or absent. Previous clinical reports of lower limb involvement include the presence of "periosteal involucrum enveloping the tibia and fibular

Table 3
Documents typical smallpox bony lesions by skeletal element and potential differential diagnoses for the involvement of each element/structure; exact types of lesions are not considered. All smallpox bone involvement is as described by Cockshott and MacGregor (1958; 1959) and Davidson and Palmer (1963), unless specific case reports are referenced. Lesion locations are listed roughly from most (top) to least (bottom) common. Where lesions are not discussed in the clinical smallpox literature, fields have been left blank.

Location	Commonality	Short-term lesion	Long-term lesion	Potential differential diagnoses (not exhaustive)
Elbows	Characteristic (bilateral)	Inflammation, destruction of epiphyses, gross and florid new bone formation, all three arm bones involved	Flail joint, premature epiphyseal fusion due to necrosis, distortion, malformation, ankylosis, acute arthritis	• Achondroplasia (Mohindra and Tuli, 1969) • Rheumatoid arthritis (Purandarnath and Douraiswami, 2011) • Tuberculosis (Aufderheide and Rodriguez-Martin, 1998; Dhillon et al., 2012) • Yaws (Waldron, 2009; Mitjà et al., 2011)
Arms	Expected (bilateral)	Inflammation, destruction, gross and florid new bone formation, all three arm bones involved	Stunted diaphyseal growth, generally bilateral	• Leprosy (Ortner, 2003) • Syphilis (Rothschild and Rothschild, 1995) • Yaws (Rothschild and Rothschild, 1995; Mitjà et al., 2011)
Wrists	Expected	Inflammation, destruction of epiphyses, new bone formation,	Premature epiphyseal fusion due to necrosis	• Leprosy (Ortner, 2003) • Rheumatoid arthritis (Wegner et al., 2017) • Tuberculosis (Aufderheide and Rodriguez-Martin, 1998)
Knees	Expected	Inflammation, destruction of epiphyses, gross and florid new bone formation, all three arm bones involved, bilateral	Flail joint, premature epiphyseal fusion due to necrosis, distortion, malformation, ankylosis, acute arthritis	• Tuberculosis (Ortner, 2003; Reuter et al., 2009) • Yaws (Mitjà et al., 2011)
Legs	Expected	Inflammation, destruction of epiphyses, gross and florid new bone formation, bilateral, tibia and fibula involved more often than the femur	Stunted diaphyseal growth, generally bilateral	• Bejel (Rothschild and Rothschild, 1995) • Leprosy (Mann and Murphy, 1990) • Syphilis (Rothschild and Rothschild, 1995) • Yaws (Rothschild and Rothschild, 1995; Mitjà et al., 2011)
Ankles	Expected	Inflammation, destruction of epiphyses, gross and florid new bone formation, all three arm bones involved, bilateral	Distortion (flattening and shortening), particularly of the calcaneus	• Leprosy (Waldron, 2009) • Tuberculosis (Aufderheide and Rodriguez-Martin, 1998) • Yaws (Mitjà et al., 2011)
Hands and Feet	Expected	Inflammation, destruction of epiphyses, gross and florid new bone formation, all three arm bones involved, bilateral	Stunted diaphyseal growth, bilateral, often symmetrical	• Bejel (Aufderheide and Rodriguez-Martin, 1998) • Leprosy (Waldron, 2009; Gunawan et al., 2021) • Rheumatoid arthritis (Auréal et al., 2021) • Syphilis (Aufderheide and Rodriguez-Martin, 1998) • Tuberculosis (Aufderheide and Rodriguez-Martin, 1998) • Yaws (Rothschild and Rothschild, 1995)
Shoulders	Rare (likely secondary pyogenic infection)	Some incidences of inflammation and suppuration (Unilateral) (Neve, 1887; Mehta,1927)		• Pyogenic osteomyelitis unrelated to smallpox
Clavicle	Rare (likely secondary pyogenic infection)	1 report of destruction and suppuration in an autopsy of a smallpox patient (Brown and Brown, 1923). 1 report of unilateral inflammation in potential archaeological case of osteomyelitis variolosa (Hall and Ponce, 2019)		• Pyogenic osteomyelitis unrelated to smallpox • Tuberculosis (Agarwal and Maheshwari, 2014)
Pelvis and hip joints	Rare (likely secondary arthritis)		1 report of arthritis of the hip-joint in an individual who had smallpox 10 years prior (Cockshott and MacGregor, 1959).	• Tuberculosis (Reuter et al., 2009)
Scapula	None expected	Rare incidences of suppurative scapulae involvement in clinical reports (appears to be unilateral, likely secondary pyogenic infections). 1 report of unilateral inflammation in suspected osteoarchaeological case of smallpox (Hall and Ponce, 2019)		• Pyogenic osteomyelitis unrelated to smallpox
Skull	None expected	1 report of destructive cranial lesions in an archaeological case with bilateral elbow changes – true aetiology unknown (Ortner, 2007). 1 report of suppurative destruction of temporomandibular joint (Cockshott and MacGregor, 1959)		• Syphilis (Rothschild and Rothschild, 1995; Ortner, 2003) • Leprosy (Anderson and Manchester, 1992)

(*continued on next page*)

Table 3 (*continued*)

Vertebrae, ribs, sternum	None expected	1 report of destruction and inflammation of axis and atlas (Huenekens and Rigler, 1926)	• Pyogenic osteomyelitis unrelated to smallpox • Tuberculosis (Ortner, 2003) • Pyogenic osteomyelitis unrelated to smallpox • Syphilis (Rothschild and Rothschild, 1995) • Tuberculosis (Aufderheide and Rodriguez-Martin, 1998; Reuter et al., 2009)

diaphyses" in a 2-year-old child (Cockshott and MacGregor, 1959: 59), and the presence of bone infection in the tibiae, fibulae, and femora of recently deceased smallpox patients (Neve, 1887; Chiari, 1893; Brown and Brown, 1923). The joints may also be affected, with ankle abnormalities seen in 18% of paediatric patients with bone involvement (Cockshott and MacGregor, 1959) and 50% of adults with typical late smallpox manifestations (Tang et al., 2021). In adult individuals with osteomyelitis variolosa, distortion of the calcaneus (such as flattening and shortening) is a commonly reported symptom, potentially due to long-term changes in mobility and weight bearing (Arora et al., 2008; Balaji, 2011; Nema et al., 2011). Davidson and Palmer (1963) also highlighted the common involvement of the calcaneus in children with typical early-stage osteomyelitis variolosa, though they do not expand on this further.

3.3. Hands and Feet

During both tuberculosis and smallpox infection, involvement of the fingers, toes and connecting joint spaces can lead to destruction of epiphyses and arrested growth. In the short-term, involvement of the hand and foot bones is patchy, lytic, and inflammatory (Cockshott and MacGregor; 1959: images pp62–63; Ortner and Putschar, 1981). In the longer-term, sufferers may exhibit short, stunted digits, usually bilaterally. This has been reported in both younger and older individuals with suspected osteomyelitis variolosa (for example individuals discussed by Cockshott and MacGregor, 1959; Ortner, 2003; Singh, 2010; Andrews and Jayan, 2011; Nema et al., 2011; Thomas, 2017) and symmetrical involvement has been noted (Cockshott and MacGregor; 1959).

3.4. Other lesions

Unlike tuberculosis, osteomyelitis variolosa does not appear to directly involve the ribs, spine, or pelvis (Cockshott and MacGregor, 1959). However, degenerative changes in the pelvic region (inclusive of the os coxae, hip joint and femoral head) have been clinically documented in a single, 20-year-old individual (Cockshott and MacGregor, 1959). Of the published archaeological individuals with potential smallpox, one documents the presence of new bone formation on the pelvis (Roberts et al., 2016). This individual also exhibited abnormalities of the ribs and spine, which are not typical of smallpox, and differential diagnoses provided included tuberculosis and other pulmonary diseases (Roberts et al., 2016).

Smallpox also does not typically involve the skull, unlike conditions such as treponemal diseases and leprosy (Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003). Clinically, cranial involvement has been reported in only one individual: an 8-year-old who began suffering from smallpox 6 months prior to assessment and displayed inflammation of the facial bones and maxilla on the right side. There has been one archaeological case, reported by Ortner (2003, 2007), where some cranial lesions were present and had undergone remodelling. However, it is unclear whether these lesions were related to the bilateral elbow involvement also reported in the same individual Ortner (2003, 2007). Ortner (2003) reports that, if caused by smallpox, these lesions may be acute, caused by close contact with skin lesions on the face and scalp.

4. Conclusion and suggested direction for future studies

It is clear given the prevalence of smallpox in the past (Koplow, 2003; Spinney, 2020), the frequency of non-adults with bone involvement reported in the 20th century, and the increasing number of modern individuals reported with long-term osteomyelitis variolosa, that smallpox is underrepresented in the archaeological record. Given that clinical studies show 2–20% of individuals exhibited bony changes – but likely only the most severe coming to hospital – it is plausible that bony changes are also apparent historically and should thus be visible archaeologically. With the aid of the diagnostic criteria, understanding of smallpox bone involvement will improve and subsequently the osteological underrepresentation of this infection will be reflected in increasing numbers of individuals reported to have suspected osteological changes consistent with having experienced, and possibly survived, smallpox.

To summarise the key bone changes involved, in the short-term, osteomyelitis variolosa typically manifests as inflammation of the long bone metaphyses and destructive remodelling of the joint surfaces and surrounding bones. The arm bones and elbow joints are those most commonly involved, usually bilaterally, but bilateral involvement of the lower limbs is also typical and should not be ignored. In the long-term, the condition can progress from initial inflammation to the presence of flail joints, stunted growth, distortion, malformation of bones, and ankylosis; these are generally still bilateral changes. Involvement of the vertebrae, ribs, scapulae, sternum, pelvis, and skull is not generally characteristic of smallpox and may point to a different or additional aetiology.

Bone changes associated with smallpox can be lifelong and therefore its diagnosis in osteoarchaeology should not be limited to non-adults. Moreover, it is important to consider that the appearance of osteomyelitis variolosa in younger non-adults is likely to be different to its appearance in older individuals, due to how the condition progresses over time. The authors have suggested that it would be highly beneficial for the identification of osteomyelitis variolosa in the archaeological record, to view the condition on a scale from its shorter-term to longer-term manifestations. The changes visible on a skeleton may fall anywhere along this scale but should roughly correlate with the changes expected at the individual's age-at-death. Given the current lack of clinical discussion about how long osteomyelitis variolosa takes to progress to its longer-term sequelae, this would be a useful avenue for future research. For now, as bone involvement likely occurs whilst cells at the secondary ossification centre are actively proliferating, then it is plausible that the most severe changes will occur around the most active physes at the time of smallpox infection. If possible, future research should explore this hypothesis, investigating bone involvement in non-adults of varying ages, to assess relationships between the involvement of certain epiphyses and age.

Another area for future research, is consideration of the lived experiences of past individuals with smallpox bone involvement, including community and medical responses, given that sequelae can be lifelong;

this is already an active area of research for other more commonly researched archaeological diseases such as leprosy and tuberculosis. An interesting aspect, already prominent in the study of leprosy, would be to assess potential exclusion and ostracization of those with visible aesthetic changes to appearance (such as scarring), and the skeletal changes following smallpox infection (and associated physical disabilities). These physical markers of smallpox, whether currently infectious or having survived a previous infection, would likely have been noticeable to the community and thus, plausibly resulted in stigma. As such, the social attitude towards, and treatment of these individuals would be of historical interest.

Whilst the presence of osteomyelitis variolosa has not yet been identified in mummified remains, despite multiple confirmed and potential smallpox infections in mummies from different temporal and geographical locations (Fig. 1), the possibility should not be overlooked. The authors would like to highlight the potential for use of radiographic imaging in future, for the non-destructive assessment of bony pathology (including osteomyelitis variolosa) in mummified remains.

Therefore, although smallpox has been long recognised as a condition which likely affected a high proportion of people, with documented outbreaks and epidemics, only limited osteological and archaeological evidence of this has yet emerged. This physical evidence is especially pertinent to our understanding of smallpox (and disease generally) in the past, as the true aetiology of plagues described in historical sources will likely always remain uncertain. This paper intends to provide a thorough review of both clinical and osteological literature, drawing together a clearer idea of smallpox manifestations, progression, and diagnostic criteria. It is hoped that this paper will improve the diagnosis of smallpox within skeletal collections and encourage further investigation into this pathology.

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